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1. Abstracts selected for Oral and Flash Presentations

1.1 Abstracts selected for Oral Presentations

1.1.1 Movement disorders

#11

A prospective pilot trial for Pallidal Deep Brain Stimulation in Huntington's Disease

Jan Vesper (1), Alfons Schnitzler (2), Lars Wojtecki (3)

1. Dept. of Functional Neurosurgery and Stereotaxy, University Duesseldorf, Duesseldorf, Germany

2. Dept of Movement disorder and neuromodulation, University of Duesseldorf, Düsseldorf, Germany

3. Dept. of Movement disorder and neuromodulation, University of Duesseldorf, Düsseldorf, Germany

Introduction: Severe forms of movement disorders in Huntington's disease are often medially refractive. Case reports suggest deep brain stimulation as treatment option, but the exact target for stimulation is under debate. We assessed procedure safety, equality of internal and external pallidal stimulation and efficacy in patients with Huntington's disease followed up for 6 months in a prospective pilot trial.

Methods: We studied 6 Huntington's Disease patients (4 chorea-dominant, 2 Westphal variant) with stable predominant movement disorder. After surgery, patients were randomly assigned either the sequence of 6 week internal/6 week external pallidum stimulation or vice versa followed by 6 months chronic pallidal stimulation. Primary endpoints were changes in the Unified Huntington's Disease Rating Scale (UHDRS) Motor Score, Chorea Subscore and Total Motor Score 4 (TMS-4) comparing internal versus external pallidum stimulation and 6 month versus baseline. Secondary endpoints assessed scores on dystonia, hypokinesia, cognition, mood, functionability/disability and quality of life. Scores were rated double-blinded using standardized video recordings. Data was analyzed on intention-to-treat basis. The trial is registered with ClinicalTrials.gov (NCT00902889).

Results: Intention to treat analysis included all 6 patients with n=3 in each treatment sequence. Internal and external pallidal stimulation was equally in terms of efficacy. Chorea sub score decreased significantly within 6 months (-5.3 (60.2%), p=0.037). Effects on dystonia were not significant over the group due to three responders (>50% improvement) and three non-responders. Westphal patients did not improve. Cognition was stable over 6 months. Mood and several functionability/disability and quality of life scores improved significantly. Eight adverse events and two additional serious adverse events were recorded. Most of them were stimulation related and under internal pallidum stimulation with bradykinesia, gait impairment, hyperkinesia and hyperthermia as the most common ones. All adverse events resolved without sequelae. No procedure related complication occurred.

Conclusion: Internal as well external pallidal deep brain stimulation occurred as safe treatment option for reduction of chorea in Huntington's Disease. Effects on chorea, dystonia and long-term effect on quality of life should be examined in further larger trials.

#18

Microelectrode recording in subthalamic nucleus deep brain stimulation: advantage or loss of time?

Ersoy Kocabicak (1), Dursun Aygun (2), Kemal Paksoy (1), Musa Onar (2), Hatice Guz (3), Omer Boke (3), Murat Kurt (4), Murat Terzi (2), Onur Alptekin (5), Onur Yildiz (2), Yasin Temel (6)

1. Department of Neurosurgery, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

2. Department of Neurology, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

3. Department of Psychiatry, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

4. Department of Psychology, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

5. Neuromodulation, Medtronic, Inc, Istanbul, Turkey

6. Departments of Neuroscience and Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

Introduction: Subthalamic nucleus (STN) deep brain stimulation (DBS) in Parkinson's disease with microelectrode recording (MER) was initially started by the Grenoble group in 1993. With the improvement of the MR imaging techniques in the following years, the dorsolateral part of the STN which is known as the motor part has started to become much better visualized. Therefore, some centers only used preoperative MRI for targeting in STN DBS and abandoned MER due to the reasons that it increases operation time and bleeding risks. In our study we present the effect of MER on operation time with the clinical results.

Methods: 18 Parkinson's disease patients (10 male- 8 female) who underwent bilateral STN DBS were included in this study. Preoperative dorsolateral STN targeting was performed by indirect-direct targeting combination and MRI-CT fusion. Number of the microelectrodes used, number of electrodes placed at the central and other trajectories were recorded separately. The time spent for MER in surgery was calculated as the time between the first microelectrode placement and the testing of the effects and side effects in macrostimulation. Early postoperative surgical and hardware-related adverse affects were noted.

Results: 117 microelectrodes were used in this study (mean: 6.5 ± 1.3). 36 microelectrodes were placed in STN. The number of permanent electrodes placed in the central trajectory was 25 (69.4%). MER extended operation time for 43.2 ± 5.5 minutes. Bleeding, contusion or infection wasn't detected in the early postoperative period.

Conclusion: STN DBS with MER extends surgical time. However, considering that we didn't use central trajectory for permanent electrode in 1/3 of our patients, we still think that MER decreases time loss and provides optimal response in situations where optimal clinical response can't be obtained intraoperatively by making the other appropriate trajectories available.

#36

STN-DBS for Parkinson's disease: correlation between the active contact electrode and oscillatory activity

Jorge Guridi (1), David Garcia-Garcia (2), Manuel Alegre (3), Maria Cruz Rodriguez-Oroz (4), Jose A. Obeso (2)

1. Neurosurgery Department, Clinica Universidad de Navarra, Pamplona, Spain

2. Neurosciences Area, CIMA, University of Navarra, Pamplona, Spain

3. Neurophysiology Department, Clinica Universidad de Navarra, Pamplona, Spain

4. Neurosciences Area, CIMA, Universidad de Navarra, Pamplona, Spain

Introduction: An excessive oscillatory activity synchronization occurs in the basal ganglia in Parkinson's disease (PD) and this has a predilection for the beta frequency band centred around 20 Hz. This activity is recorded in the dorsal portion of STN. This study analyzes the correlation between this beta activity and the active contact used in STN-DBS

Methods: Localization was determined in 30 patients with PD and treated with STN-DBS surgery. MRI preop and postoperative has been coregistrated and precise placement of each electrode contact evaluated in correlation with the stereotactic volume created based in the AC-PC line, thalamic height and III ventricle width. A 3-dimensional (3-D) atlas STN model was created based in Morel atlas and coregistrated with the stereotactic volume created. Finally the electrode active contact was accurately located within or out of the STN. Active contact is defined as the contact that induce the best clinical benefit reducing the motor UPDRS and the study has been performed only in monopolar stimulation contacts. Local field potentials recorded oscillatory activity 3-4 days after implantation surgery with the patient in "off" and "on" dopaminergic condition.

Results: Active contact electrode was placed in the dorsolateral portion of STN (X: 11.52, Y: 1.22 posterior mid point, Z: 1.08 below the AC-PC line). Beta oscillatory activity was recorded (LFP) in the dorsal portion of the nucleus. There was no statistical difference between both.

Conclusion: Active contact electrode and beta oscillatory activity are localized in the motor portion of STN. The results indicates that stimulating the dorso-lateral oscillatory region leads to an effective clinical outcome for STN-DBS surgery.

#37

Resting state cortical oscillations of Parkinson's disease patients without and with subthalamic deep brain stimulation, a MEG study

Cao Chunyan (1), Jang Tianxiao (2), Li Dianyou (3), Zhan Shikun (4), Firat Ince Nuri (2), Sun Bomin (4)

1. Department of Functional Neurosurgery, Ruijin Hospital, Shanghai, China

2. Department of Biomedical Engineering, University of Houston, Houston, China

3. Department of Functional Neurosurgery, Ruijin Hospital Shanghai Jiaotong University, School of Medicine, Shanghai, China

4. Department of Functional Neurosurgery, Ruijin Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China

Objective: To investigate the modification to cortical oscillations of Parkinson's disease (PD) patients by the subthalamic deep brain stimulation (STN-DBS).

Methods: Detected with magnetoencephalography (MEG), the cortical spontaneous oscillations of PD patients undergoing STN-DBS at stimulation ON and OFF statuses were compared, accompanied by UPDRS III evaluation. Same features of PD patients without surgery and healthy controls were also compared,

Results: In PD patients without surgery, the cortical average frequency slowed down and average power incremented significantly, with an increase in relative power in θ , and a parallel decrease in β and γ over temporal and occipital cortex relative to healthy controls; the UPDRS III rigidity score correlated with average frequency of frontal, and also correlated with the relative power of β and γ in frontal. In PD patients with STN-DBS, the average frequency increased significantly at stimulation ON comparing to stimulation OFF status, accompanied by drop in the relative power of δ and rise in the relative power of β over the whole cortex; at stimulation ON status, the UPDRS III rigidity and tremor scores correlated with the relative power of α over left parietal.

Conclusion: STN-DBS improves the symptoms of PD by suppressing the synchronization of α in left somatomotor region.

#53

Deep Brain Stimulation of the internal globus pallidus in severe Tourette Syndrome.

Anouk Smeets (1), Annelien Duits (2), Albert Leentjens (3), Mayke Oosterloo (4), Veerle Visser-Vandewalle (5), Birgit Plantinga (6), Yasin Temel (1), Linda Ackermans (1)

1. Neurosurgery, Maastricht University Medical Centre, Maastricht, Netherlands

2. Psychiatry and Psychology, Maastricht University Medical Centre, Maastricht, Netherlands

3. Department of psychiatry and psychology, Maastricht University Medical Centre, Maastricht, Netherlands

4. Department of neurology, Maastricht University Medical Centre, Maastricht, Netherlands

5. Department of Functional and Stereotactic Neurosurgery, University of Cologne, Cologne, Germany

6. Department of neuroscience, Maastricht University Medical Centre, Maastricht, Netherlands

Introduction: Tourette Syndrome (TS) is a complex childhood-onset neuropsychiatric disorder characterized by multiple motor- and vocal tics. The exact pathophysiology is unknown but TS is thought to result from dysfunction of the basal ganglia and the related thalamocortical circuits. Deep Brain Stimulation (DBS) of different output or relay stations in this circuit has been proposed as a therapeutic option for severe therapy refractory TS, including the limbic internal globus pallidus (GPi). In this case series we describe the effects of limbic GPi stimulation on tics and associated behavioural disorders, whereas adverse events and cognition are carefully monitored.

Methods: Five patients with severe therapy refractory TS were selected for bilateral DBS of the limbic GPi. Patients were evaluated twice: once in the month before surgery and once after surgery, on all primary and secondary outcome measures, as well as on cognition. Follow-up duration was variable, but at least 12 months. The primary outcome measure was tic severity, assessed by the Yale Global Tic Severity Scale (YGTSS), the modified Rush Video-Based Tic Rating Scale (mRVRS) and the amount of video-tics in 10 minutes.

Secondary outcome measures were the effects on potentially associated behavioural disorders, such as Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive Compulsive behavior (OCb), as well as mood (depression and anxiety). A neuropsychological examination was performed to assess cognition. Complications and side-effects related to the surgery or the stimulation were carefully monitored. The final position of the active contacts of the implanted electrodes was visualized.

Results: Five patients, three male and two female were selected for DBS of the limbic GPi between 2010 and 2013. Follow-up duration ranged from 12 to 38 months (SD 13.7). The mean age of the group was 41.6 years (SD 9.7) and the mean disease duration was 33.2 years (SD 8.9). The position of the implanted electrodes showed adequate anatomic localization in all patients. The average postoperative score on the YGTSS was significantly lower than the preoperative score (42.2 ± 4.8 versus 12.8 ± 3.8 , $P=0.043$). There was also a significant reduction of 80.9% on the total amount of video-rated tics (259.6 ± 107.3 versus 49.6 ± 24.8 , $P=0.043$) and of 46.2% on the mRVRS (13.0 ± 2.0 versus 7.0 ± 1.6 , $P=0.041$). There was no significant difference between pre- and postoperative secondary outcome measures. However, on an individual level (four of the four patients with elevated levels prior to surgery) we found a positive trend for an improvement in obsessive-compulsive behaviour. Cognitive re-assessment revealed no changes. Complications included one infection of the pulse generator and one case of lead traction. Side effects were apathy and passive behaviour in two patients, and weight loss and agitation in one other patient.

Conclusion: Our findings suggest that stimulation of the limbic GPi is effective in reducing tic severity, and possibly also OCb, in therapy refractory Tourette patients. This is in line with most previous reports targeting this area. The absence of effect on ADHD, anxiety and depression could be due to the fact that these symptoms were absent or mild in our patients prior to surgery, and the low power of this sample. So far, DBS of the limbic GPi seems safe from a cognitive point of view. Adverse events and side-effects related to the stimulation were minor in this study. Our study adds to the little available evidence suggesting that limbic GPi stimulation could be effective in severe refractory TS. We are cautious in over-interpreting the data, but based on this experience and other published evidence, we will continue targeting the limbic GPi as a first choice in future DBS therapy in refractory TS patients.

#76

Saccade-related modulation of beta oscillation in the human internal globus pallidus

Akihiro Yugeta (1), Robert Chen (2), William D. Hutchison (3)

1. Department of Neurology, University of Tokyo Hospital, Tokyo, Japan

2. Department of Neurology, University of Toronto, Toronto, Canada

3. Department of Physiology, University of Toronto, Toronto, Canada

Introduction: Antisaccades require inhibition of reflexive responses towards visual cues, and strong initiation of saccades away from visual cues. Studies in monkeys reported more prominent pallidal cell firing during antisaccades than prosaccades (Yoshida and Tanaka 2009). We reported beta-SRDs in the subthalamic nucleus (STN) of Parkinson's disease patients during saccades. Since the STN projects to the internal globus pallidus (GPi) we expect that beta-SRDs also occur in the GPi. Although saccade abnormalities caused by GPi lesions have been reported, saccade-related GPi oscillations has not been studied in human. Objective: To investigate whether oscillations in the GPi in primary dystonia patients are modulated by saccades, and to compare the responses to prosaccades and antisaccades. We hypothesize that antisaccades would produce more prominent saccade-related beta-band desynchronization (beta-SRD) than prosaccade.

Methods: We recorded the local field potentials from DBS electrodes implanted in the GPi in 7 primary focal dystonia patients 1 to 5 days after electrodes implantation when the leads were externalized. The patients performed visually guided prosaccade and antisaccade tasks. We analyzed the Molet wavelet power spectrum averaged on saccade onset using bipolar derivations.

Results: The beta-SRDs were observed in the GPi just prior to and during saccades in 6 patients. Beta-SRD were observed in the contralateral or the ipsilateral GPi, and in some patients bilaterally. The onsets, durations, and amplitudes of beta-SRDs were not different between prosaccades and antisaccades.

Conclusion: Beta-SRDs were observed in the GPi of dystonia patients. Unlike beta-SRD in the STN, beta-SRDs in the GPi were not related to inhibition of unwanted saccades, because they were not different between prosaccades and antisaccades. While it is well known that the basal ganglia output from the substantia nigra pars reticulata strongly inhibits the superior colliculus, our results suggest that the basal ganglia output from the GPi, especially the beta-band desynchronization, may also be involved in control of saccades.

#94

Cerebellar peduncle stimulation reduces symptoms of dystonia in patients with cerebral palsy treated due to spasticity

Paweł Sokal (1), Marek Harat (1), Marcin Rudas (1), Łukasz Szyłberg (2), Marcin Rusinek (1)

1. Neurosurgery, Military Research Hospital, Bydgoszcz, Poland

2. Pathology, Collegium Medicum Univ Nicolaus Copernicus, Bydgoszcz, Poland

Introduction: Cerebellar Peduncle Stimulation (CPS) is a neuromodulative method of treatment of spasticity. Bilateral CPS is applied in young patients with cerebral palsy (CP). In these patients symptoms of spasticity coexist with symptoms of focal or segmental dystonia, which can cause chronic pain. We performed the study in order to determine the efficacy of CPS.

Methods: We examined 10 patients with CP treated with CPS due to spasticity in years 2006-2012. We compared Ashworth scores of spasticity, VAS score of pain and UDRS (Unified Dystonia Rating Scale) score before CPS and after in follow-ups lasting from 2 to 11 years in these patients. We also asked them or their parents on the impact of CPS on pain syndrome coexisting with spasticity and dystonic involuntary movements.

Results: We received statistically significant reduction of spasticity in upper extremities (median : from 3 to 1,5 in Ashworth scale) in 8 patients ($p=0,01$), in lower extremities in 7 patients (median : from 3 to 1,75 in Ashworth scale) ($p=0,02$). Better results were observed in elder patients over 26 years old. Decrease in intensity of symptoms of dystonia measured in consecutive parts of UDRS in 7 patients was statistically significant (median: from 1,6 to 1,0) ($p=0,017$). Symptoms of focal dystonia (involuntary movements of neck and hand) were decreased by 45% and 40% respectively in 50% of patients, in others reduction was ranging from 25 to 33%. Duration of these symptoms in 50% of patients was reduced by 40%. Relief in pain was not statistically significant.

Conclusion: Chronic bilateral CPS aimed for spasticity treatment not only decreases muscular tone in quadriplegic or paraplegic patients with CP but also is associated with reduction of symptoms of focal or segmental dystonia.

#102

Assessment of neural activation using directional deep brain stimulation leads

Christopher Butson (1), Lalit Venkatesan (2)

1. Biomedical Engineering, University of Utah, Salt Lake City, United States

2. Neuromodulation, St Jude Medical, Plano, TX, United States

Submitter: Mr Butson Christopher (US)

Introduction: Deep brain stimulation (DBS) therapy is applied using multi-contact leads that are implanted in subcortical regions. Commercially available DBS leads contain cylindrical electrodes that provide relatively uniform current spread radially outward. However, for more localized stimulation it may be desirable to apply current preferentially in one direction, for example to steer current toward one anatomical region that mediates therapeutic effects while avoiding another region where stimulation causes side effects. A potential solution to this would be to divide each cylindrical electrode into multiple radial segments and to activate these segments independently. In this study we used a computational model to evaluate whether a novel DBS lead could provide preferential activation using such segmented electrodes.

Methods: A previously published computational model of DBS (Butson et al, 2007) was used to characterize neural activation for a novel lead design with two standard cylindrical electrodes and six directional electrodes. All electrodes are 1.5 mm long (along the axis of the lead) and 1.27 mm diameter. Of the four "rows" of electrodes in the directional lead, two are standard cylindrical contacts and two are divided into thirds, where each contact has an arc length of 1.1 mm. A three-dimensional finite element model of the electrodes and surrounding tissue medium was created in COMSOL version 4.3 to compute the electric fields produced during stimulation with the standard cylindrical electrodes as well as segmented electrodes. Multi-compartmental models of myelinated axons were used to predict the neural response. This model takes into account the time-dependence of the stimulation waveform and the electrical properties of tissue encapsulation surrounding the lead. The volume of tissue activated (VTA) were determined for current-controlled stimulation (130 Hz, 60 μ sec, -.25 mA to -5 mA), and the size and radial directionality of VTAs for each electrode design was assessed.

Results: The extent and direction of neural activation varied depending on the number of active contacts. Standard cylindrical electrodes produced VTAs that were roughly spherical. However, when individual segmented electrodes were activated, the VTA was displaced toward the side of the lead with the active contact, creating preferential activation on one side. Compared to the standard cylindrical electrode, VTA sizes were larger when fewer contacts were used. Stimulation with a single directional electrode contact at common stimulation settings (2.5mA, 60 μ sec, 130Hz) generated VTAs that were 60% larger (196mm³) than the standard cylindrical electrode (179mm³); stimulation with two adjacent active directional contacts generated VTAs that were 46% larger (166mm³); stimulation with three active directional electrodes generated VTAs that were 36% larger (196mm³). When three directional electrodes in one row were simultaneously activated, the VTA was of a very similar location and shape compared to a standard cylindrical electrode.

Conclusion: This lead design could provide comparable capabilities to existing leads, but more precise activation of targeted regions and better energy efficiency if incorporated into existing DBS systems.

#106

STUDY OF SUBTHALAMIC MOTOR CORTICAL CONNECTIVITY IN PARKINSON'S DISEASE AS PREDICTIVE FACTOR FOR DEEP BRAIN STIMULATION

Rebeca Conde (1), Antonio Gutierrez (1), Irene Martinez (2), Ignacio Rubio (2), Vicente Belloch (3), Carlos Botella (1)

1. Neurosurgery, Hospital Universitari i Politècnic La Fe, Valencia, Spain

2. Neurology, Hospital Universitari i Politècnic La Fe, Valencia, Spain

3. Radiology, Hospital Universitari i Politècnic La Fe, Valencia, Spain

Introduction: Identification of the motor part of the subthalamic nucleus as part of the pre-surgical workup could minimize adverse effects and improved motor effects. We describe the subthalamic patterns connectivity with IRM-DTI analysis and make a correlation study of DTI patterns with hyperdirect pathway with MER and clinical effect of DBS therapy.

Methods: We analyzed 25 patients, 90 MER, and 50 DBS. Stereotactic procedure with Leksell frame in 18 and Medtronic Nextframe in 17.

Alpha Omega software microguide system for MER. All patients have a study with T1 and T2 3T IRM, 3D CT scan co-register (stealthstation S7), sequential intraoperative Oarm, and postoperative CT scan. DTI 3T IMR Philips 32 gradients in StealthViz and AMIRA System computer processed. We made an analysis of subthalamic points of connectivity with motor cortical surface.

Results: The premotor cortical connectivity is 30% anterior and 70% central, and motor connection is 100% posterior. The circuit substantia nigra, red nucleus, mesencephalum and cerebellum is constant. There is a intrathalamic connection between motor and premotor tracks. The part of subthalamic nucleus connected with the motor system is central and lateral.

Conclusion: We could study the level of segregation of the STN motor part, which is relevant for the planning of STN DBS procedures. We observe a correlation with motor recruitment and better clinical results in patients with DBS sets near motor connectivity points.

#157

Technical considerations and outcome of DBS for dystonia in very young children

Ismail Ughratdar (1), Eunice Chan (2), Daniel Lumsden (2), Margaret Kaminska (2), Jean-Pierre Lin (2), Keyoumars Ashkan (1), Richard Selway (1)

1. Neurosurgery, King's College Hospital, London, United Kingdom

2. Paediatric Neurology, Evelina London Children's Hospital, London, United Kingdom

Introduction: Deep brain stimulation (DBS) for medically refractory dystonia is an effective intervention to improve quality of life in children, but timing of DBS surgery remains controversial and is often offered late in the course of the disease when fixed deformities are common. There is limited worldwide experience of DBS in children, especially under the age of seven years. We review the outcomes and discuss the surgical considerations from our experience of 21 children under the age of seven who underwent bilateral DBS for dystonia.

Methods: Database audit of all DBS cases under the age of seven years performed at a single institute. 21 children of median age 5.4 years (range 3.0-6.8 years) with primary dystonia (3/21), secondary dystonia (15/21) and neurodegeneration (3/21) underwent 29 DBS-related surgeries between 2005 and 2014. Age of dystonia onset ranged from birth to 60 months (median 6.5 months), with median duration of life lived with dystonia 4.4 years prior to surgery. At baseline, 10/20 cases were on two or more medications for dystonia management. Follow-up duration for this cohort ranged from 3 to 81 months (median 45 months).

Results: At last review, DBS was included as an active treatment in 19 cases and the only active management strategy in 4/19 cases. The three neurodegenerative cases of Pantothenate Kinase Associated Neurodegeneration (PKAN) had 5-6 medications in addition to DBS, and those with primary or secondary dystonias had a median of 2 medications with DBS management. Dystonia outcomes as measured by Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) will be discussed. 3/21 children died (1 PKAN, 2 secondary dystonia secondary to parainfectious nigrostriatal necrosis) at 3-4.5 years following DBS surgery. Early hardware complications (onset <6 months following surgery) occurred in 8 surgeries, with 5/8 cases of seroma/cellulitis that resolved with antibiotic treatment, 1 infected system on long-term antibiotics and 2 infected systems requiring explantation of device and electrodes. Late hardware complications occurred in 5 cases including electrode migration requiring electrode replacement (1/21), faulty electrode conservatively managed (1/21), and an infected system/skin erosion prompting device explantation (3/21) or 14.2% of cases. The infection rate was higher in subsequent surgeries for device or electrode replacement (3/8) compared to 2/21 primary surgeries for device implantation or 9.5% of cases. Battery replacement was frequently required due to high stimulation settings in the earlier DBS programme stages, replaced by smaller rechargeable batteries. Other complications included inadvertent switching off of device (3/21), recharger problems (4/25), noncompliance with recharging (1/21), and request for deactivation of the DBS system due to perceived lack of efficacy (2/21), one case being switched on again 6 months later.

Surgical technical considerations for this age group include (i) position of the IPG often in the abdomen (ii) requirement of longer lead extension wires to allow for body growth (iii) reduced tightening on frame fixation to accommodate decreased skull thickness, average 3.21mm (Range 1.94-5.12mm) (iv) variations in anatomy (e.g. narrow third ventricle, plagiocephaly, presence of focal pathologies) rendering atlas-based targeting inaccurate.

Conclusion: DBS in very young children is effective in the management of severe dystonia. Infection rates are not as high as have been previously reported, and surgical technique can be appropriately adapted down to the age of 3 years. Rechargeable devices seem to be well tolerated and managed by carers. Apart from minor technical aspects that need to be considered, age should not be a barrier to DBS implantation.

#176

Fiber tractography-guided stereotactic thalamic surgery for intractable tremor

Susumu Sasada (1)

1. Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Introduction: The ventralis intermedius (VIM) nucleus has been targeted for suppression of intractable tremor for many years. However, it has recently been reported that the ventro-oralis posterior nucleus (VOP) or the posterior subthalamic area (PSA) might be useful alternative targets. These nuclei are not distinguishable using conventional imaging modalities. However, a modality to distinguish them is now available. Using diffusion tensor imaging (DTI)-based fiber tractography (FT), some individual fiber tracts in the ventrolateral thalamus or the white matter can be visualized. The purpose of this study was to investigate the effectiveness of DTI-FT-guided stereotactic thalamic surgery for intractable tremor.

Methods: Eleven patients with intractable tremor underwent stereotactic thalamic surgery between May 2012 and April 2014. A conventional indirect targeting method without DTI-FT was performed in six patients (non-FT group). A new direct targeting method guided by DTI-FT was performed in five patients (FT group). Preoperative DTI, T1- and T2-weighted sequences were performed using 3T-MRI for all patients. Four fiber tracts around the ventrolateral thalamic nuclei were drawn (cerebello-thalamo-premotor cortical fiber tract, cerebello-thalamo-primary motor cortical fiber tract, spino-thalamo-somatosensory cortical fiber tract, and pyramidal tract). In the FT group, the cerebello-thalamo-premotor cortical fiber tract in the thalamus was targeted. The final location of thalamotomy or the DBS lead was determined using microrecording and test stimulation. Preoperative and postoperative tremor were evaluated using the Fahn-Tolosa-Marin (FTM) tremor rating scale. Adverse effects after surgeries were also observed.

Results: The FTM tremor rating scale scores were decreased by over 75% in all patients. There were no perioperative adverse effects. Active DBS contacts and lesion sites were placed on the cerebello-thalamo-premotor cortical fiber tract in both the non-FT group and FT group.

Conclusion: The cerebello-thalamo-premotor cortical fiber tract might be an optimal target in the thalamus for tremor suppression. DTI-FT can visualize and evaluate individual nerve fiber trajectories. Although nuclei in the thalamus have been targeted in stereotactic surgery for intractable tremor, hereafter, it is expected that fiber tracts can be targeted with DTI-FT. DTI-FT was useful in planning stereotactic surgery for intractable tremor.

#182

A functional assessment of essential tremor treated with bilateral or unilateral surgery

Robert Dallapiazza (1), Diane Huss (2), Binit Shah (3), Madaline Harrison (3), W. Jeff Elias (1)

1. Neurosurgery, University of Virginia, Charlottesville, United States

2. Physical Therapy, University of Virginia, Charlottesville, United States

3. Neurology, University of Virginia, Charlottesville, United States

Introduction: Thalamic DBS is the primary treatment for medication-refractory essential tremor. Recently, the development of transcranial, high-intensity focused ultrasound has renewed interest in thalamic lesioning. Critics of thalamic lesioning cite that only unilateral procedures can be safely performed, leaving significant tremor symptoms on the untreated side. The purpose of this study is to compare functional outcomes in ET patients treated with either bilateral Vim DBS or unilateral FUS thalamotomy.

Methods: This study is a retrospective analysis of ET patients treated at the University of Virginia. Forty patients with bilateral Vim DBS and 15 patients with unilateral FUS treatments met the study criteria. Patients were evaluated preoperatively and postoperatively using the Clinical Rating Scale for Tremor (CRST) and Quality of Life in Essential Tremor Questionnaire (QUEST). Total CRST, hand sub-score, and axial tremor were used to assess tremor. The primary functional outcomes were measured with CRST Part C disability sub-score and QUEST.

Results: Baseline tremor scores were not significantly different between the two groups (CRST 61.5 versus 55, $p = 0.21$) except for Part A observed tremor sub-score of the CRST (20 versus 13.4, $p = 0.02$) indicating a higher degree of observed tremor. Baseline QUEST scores were higher (more severe) for patients undergoing DBS (51.9 versus 37.5, $p = 0.02$). After surgery, there were no differences in hand tremor sub-score comparing bilateral Vim DBS and unilateral FUS treatment (4.6 and 3.9 versus 5.5 [treated hand score], $p = 0.26$ and 0.45).

Postoperative total CRST scores, Part A observed tremor, and Part B tasks and drawing were significantly improved for patients undergoing bilateral Vim DBS compared to unilateral FUS treatment (10.5 versus 24.3, $p < 0.01$; 3.25 versus 8.7, $p < 0.01$; and 5.4 versus 12.7, $p < 0.01$; respectively). Part C disabilities sub-score and QUEST scores were not different comparing bilateral Vim DBS to unilateral FUS treatment (2.0 versus 2.8, $p = 0.34$ and 12.9 versus 12.0, $p = 0.87$).

Conclusion: This data suggests that bilateral DBS improves overall tremor significantly more than unilateral FUS treatment as expected from bilateral treatments, however FUS is equally effective in tremor reduction of the upper extremity. Despite a greater magnitude of overall tremor reduction with bilateral treatment, there is no difference in disability or quality of life compared to unilateral treatment. Further studies on larger numbers of patients are necessary to confirm these findings.

#184

NSTAPS trial: 3-year follow-up interim analysis

Netherlands Subthalamic And Pallidal Stimulation trial in Parkinson's disease

Vincent Odekerken (1), P. Rick Schuurman (2), Rob de Bie (3)

1. Neurology department, Academic Medical Center, Amsterdam, Netherlands

2. Neurosurgery, Academic Medical Center, Amsterdam, Netherlands

3. Neurology, Academic Medical Center, Amsterdam, Netherlands

Introduction: Bilateral Globus Pallidus (GPi) deep brain stimulation (DBS) and subthalamic nucleus (STN) DBS are both effective treatments for advanced Parkinson's disease. One-year results of the Netherlands SubThalamic and Pallidal Stimulation (NSTAPS) study showed no difference in functional improvement on the time-weighted AMC Linear Disability scale and no difference on a composite score for cognition, mood, and behavior. Secondary end points including motor symptoms and disability in off-medication-phase improved significantly more in the STN group after 1 year. This difference in effectiveness between GPi DBS and STN DBS has not yet been established after long term follow-up.

Methods: We performed a randomized controlled trial in the period 2007-2012 and recruited patients in five out of six Dutch hospitals that perform DBS for idiopathic PD. Patients and raters were blinded for treatment allocation. Three year follow-up was planned to be completed in April 2014, but due to logistics the last follow-up visits will take place in June 2014. This poster is based on an extra interim analysis for the ESSFN in Maastricht. Baseline characteristics and 1-year results have been previously published

Results: The Unified Parkinson's Disease Rating Scale (UPDRS) motor examination showed an improvement of 10.5 ± 15.0 (SD) in the GPi group (N=43) after three years and 16.5 ± 15.7 in the STN group (N=39, between group difference $p=0.08$). No between-group differences were found on the UPDRS motor examination in on phase (GPi group improvement -5.3 ± 10.7 , STN -1.7 ± 12.6 , $p=0.16$). No differences were seen on the UPDRS-activities of daily living subscale or Parkinson's disease quality of life questionnaire. No differences in morbidity, loss of relation, loss of job, psychosis, depression or anxiety were noted.

Conclusion: This analysis is a interim analysis for the ESSFN in Maastricht. More complete data will be available after the 3-year follow-up is complete in June 2014. We did not demonstrate a difference between GPi and STN DBS regarding: cognitive, mood and behavioral effects, adverse events. We did demonstrate a trend towards a difference between GPi and STN DBS regarding: UPDRS ME in off phase, favoring STN DBS. This difference however is not yet statistically significant in this late interim analysis .

#197

Successful pallidotomy using remote microelectrode mapping

Jason Moyer (1), He Huang (2), Fred Haer (3), Andrei Barborica (4), Erwin Montgomery (5), Leland Albright (6)

1. Business Development, FHC, Inc., Bowdoin, ME, United States

2. Computer Science, Greenville Neuromodulation Center, Greenville, PA, United States

3. Administration, FHC, Inc., Bowdoin, ME, United States

4. Administration, FHC Europe, Bucharest, Romania

5. Neurology, Greenville Neuromodulation Center, Greenville, PA, United States

6. Neurological Surgery, University of Wisconsin Hospital, Madison, WI, United States

Introduction: Ablative and Deep Brain Stimulation functional stereotactic surgeries offer remarkable benefits for patients, but the required technology and expertise often are unavailable. The case presented describes a system that requires a neurosurgeon to place fiducials and obtain a MRI and/or CT scan in order to offer stereotactic/functional surgery such as DBS or ablation.

Methods: Based on the imaging, a patient-unique frameless platform was fabricated to create a trajectory to the desired target. A technician traveled to Kijabe Mission Hospital in Kenya Africa with the frame, a system for microelectrode recordings, a radiofrequency lesion generator and electrode, and a computer-based monitoring system for automated analysis of the microelectrode recordings. An intraoperative neurophysiologist in Greenville PA, USA monitored and controlled the microelectrode recordings and directed target identification in real-time via the Internet. The monitoring system greatly reduced bandwidth requirements making Internet transmission feasible. In addition, the computer system had sufficient on-board "intelligence" to allow the local neurosurgeon to continue the surgery in the event of Internet failure. In addition, the remote intraoperative neurophysiologist directed the ablation. The computer monitoring system utilized software that automatically identified and alerted the users to the presence of neuronal action potentials (spikes) in the microelectrode recordings. The software was based on the inherent statistical structure of the time series of recording amplitudes and methods based on regression towards the mean (US patent no. 7,957,793 B2). The spikes were then automatically discriminated to indicate the number of neurons in the recording site and the discharge frequencies of each neuron. The software identified 6 heuristics (US patent no. 7,957,793 B2) that were fitted to a 6-dimensional space. Unsupervised n-dimensional cluster analysis was used to discriminate the waveforms (US patent 8,150,795 B2). In addition, ongoing raster presentations of the spikes demonstrated the pattern of neuronal activities. The local user was outfitted with a motion sensor to detect sensorimotor stimulation and the computer system then created peri-event rasters and histograms to determine whether the neurons were responsive to sensorimotor driving. This information acquired at multiple locations in the microelectrode trajectory allowed precise mapping and consequently, determination of the trajectory most optimal for ablation.

Case description: The patient was a 25-year- female with a 17-year history of severe generalized chorea that was unresponsive to all reasonable medication therapies. The chorea was severe enough to result in significant self-injury. Under sedation, a set of four fiducials was implanted (FHC Inc., Bowdoin, ME, USA) and MRI and CT scans were obtained. A stereotactic frame platform was constructed for a left-sided pallidotomy (STarFix™, FHC Inc., Bowdoin, ME, USA) and sent with a technician along with a microelectrode recording system (neuroCase, FHC Inc., Bowdoin, ME, USA), a radiofrequency lesion generator and electrodes (Cosman Medical Inc., Burlington, MA, USA), and the computer analysis and monitoring system (Distance Expert®-Surgical, Greenville Neuromodulation Center, Greenville, PA, USA). The surgery was conducted under dexmedetomidine. The first trajectory demonstrated that it was not optimal for ablation. A second trajectory was required which demonstrated neurons responding to sensorimotor driving of the contralateral upper extremity. The radiofrequency lesion electrode was placed in the second trajectory. The anesthesia was lighted and low frequency stimulation at 2 pps (pulse width of 2 milliseconds and a voltage of 2.5 volts) increased the chorea. High frequency (150 pps) slightly reduced

the chorea. A reversible heating (50 degrees centigrade for 30 s) reduced the chorea and was well tolerated. A permanent lesion was created by first heating to 70 degrees for 60 s.

Results and conclusion: No untoward effect was noted and the lesion was increased by heating to 80 degrees for 60 s. This lesion produced slight benefit. The electrode was pulled back 4 mm and the process repeated. At this time, there was a significant reduction in chorea. By the third day post-operatively, there was remarkable improvement of the right-sided chorea without any adverse effects.

#200

Deep brain stimulation and its effect on the cost of Parkinson's medications

David Rowell (1), Hong Son Nghiem (2), Peter Silburn (3), Terry Coyne (3), Luke Connelly (3)

1. Asia-Pacific Centre for Neuromodulation, The University of Queensland, Brisbane, Australia

2. CONROD, The University of Queensland, Brisbane, Australia

3. UQ Centre for Clinical Research, The University of Queensland, Brisbane, Australia

Introduction: The clinical literature reports that deep brain stimulation (DBS) can reduce the cost of pharmaceuticals required to treat Parkinson's disease between 30% and 80%. Consequently, reduced medication costs are frequently attributed to DBS. However, these cost estimates have often been derived from small cohort studies with brief follow-up periods. DBS was introduced into Australia in 2002. Our aim is to conduct a whole of health-system analysis of the effect that DBS has on the cost of medications used to manage Parkinson's disease.

Methods: Australia's national health insurer Medicare Australia reports monthly data for the consumption of all subsidized pharmaceuticals and medical services. Sixty medications used to treat Parkinson's disease, as well as seven surgical procedures and one medical procedure associated with DBS were identified. These time-series data ($t = 267$) were downloaded and analyzed as follows. Since time-series regression can generate spurious results due to trend-related correlation, our statistical models were estimated in first differences. The dependent variable was the aggregate cost of Parkinson's medication. The medical procedure, Programming of the DBS neurostimulator, was selected as the explanatory variable of interest.

Results and conclusion: We can report a negative and statistically significant coefficient, which is consistent with the hypotheses that the introduction of DBS in 2002 has reduced the cost of medications used to manage Parkinson's disease.

#227

Directional Deep Brain Stimulation improves the therapeutic window: an Intraoperative Double-Blind Pilot Study

Claudio Pollo (1), Alain Kaelin-Lang (2), Markus Oertel (3), Lennart Stieglitz (4), Michael Schüpbach (5)

1. Neurosurgery, University Hospital, Inselspital, Bern, Bern, Switzerland

2. Neurology, Hospital Lugano, Lugano, Switzerland

3. Neurosurgery, University Hospital, Inselspital, Bern, Bern, Switzerland

4. Neurosurgery, University Hospital Zürich, Zürich, Switzerland

5. Neurology, University hospital, Inselspital, Bern, Bern, Switzerland

Introduction: Although DBS has shown to drastically improve symptoms of a variety of neurological conditions, the occurrence of acute disabling or even chronic side effects may limit the ability to deliver adequate current necessary to reach the maximal benefit. Computed models have suggested that reduction in electrode size and the ability to provide directional stimulation could increase the efficacy of DBS therapies. However, this has never been demonstrated in human. The objective of the present study is to assess the effect of directional stimulation on the current threshold window between positive and side effects, defined as the therapeutic window (TW), compared to omnidirectional stimulation.

Methods: We applied directional stimulation intraoperatively in the STN of 11 patients with Parkinson's disease and in the Vim of 2 with essential tremor selected to undergo DBS. 3 different directions of stimulation as well as omnidirectional stimulation were assessed at the trajectory chosen for implantation of the definitive electrode.

Results: All except for one patient, showed a benefit of directional stimulation compared to omnidirectional. A best direction of stimulation was observed in all the patients. The TW in the best direction of 1.93 mA:1.0–2.9 mA) was wider ($p = 0.003$) than the 2nd best direction (1.43 mA:0.2–2.9mA) and than the 3rd best direction (0.96mA:0–2.1mA) ($p = 0.002$). Compared to omnidirectional direction, TW in the best direction was 41.3% wider ($p=0.037$). The current threshold producing meaningful therapeutic effect in the best direction was 0.67 mA (0.3–1.0 mA) and was 43% lower ($p=0.002$) than in omnidirectional stimulation. No complication due to insertion of the directional electrode or stimulation were encountered in the directional test phase.

Conclusion: Intraoperative directional DBS applied in the STN and the Vim with a reduced electrode size significantly widened the therapeutic window and lowered the current needed for beneficial effects, compared to omnidirectional stimulation. The observed side effects related to direction of stimulation were consistent with the anatomical location of surrounding structures. This new approach opens the door to an improved DBS therapy, not only in currently used targets, but also in emerging targets. It could and even generate new targets for stimulation. Chronic implantation is further needed to confirm these findings.

#237

DBS in STN and Vim for tremor. Are we stimulating a unique structure?

Michael Fiechter (1), Andreas Nowacki (2), Michael Schüpbach (3), Ines Debove (4), Lennart Lachenmayer (4), Roland Wiest (5), Markus Oertel (6), Claudio Pollo (7)

1. Neurosurgery, University hospital, Inselspital, Bern, Bern, Switzerland

2. Neurosurgery, University Hospital, Inselspital, Bern, Bern, Switzerland

3. Neurology, University hospital, Inselspital, Bern, Bern, Switzerland

4. Neurology, University Hospital, Inselspital, Bern, Bern, Switzerland

5. Neuroradiology, University Hospital, Inselspital, Bern, Bern, Switzerland

6. Neurosurgery, University Hospital, Inselspital, Bern, Bern, Switzerland

7. Neurosurgery, University Hospital, Inselspital, Bern, Bern, Switzerland

Introduction: DBS in the subthalamic nucleus (STN) or the ventral intermediate nucleus (Vim) has shown to be effective for the treatment of tremor in patients suffering from Parkinson disease (PD) or essential tremor (ET). Normally patients with PD are implanted and stimulated in the STN whereas patients with ET are implanted and stimulated in Vim of the thalamus. However, the optimal site of stimulation is still debated. Retrospective studies on electrode position in the Vim pointed out the possibility of stimulated contacts below the thalamus. Similarly, studies performed in the STN reported efficiency above and medial to it. In this study, we retrospectively propose to calculate the site of stimulation of patients implanted in the STN and Vim for PD and ET respectively and discuss the possible common structure involved in DBS for tremor after surgery. Recently, diffusion tensor imaging (DTI) studies have shown that stimulation of the dentatorubrothalamic tract (DRTT) crossing this area could be the optimal point of stimulation. For this reason we performed a retrospective analysis of the position of the active contacts of the electrodes in tremor patients with Parkinson disease and essential tremor with the help of the new OPTIVISE software.

Methods: 38 patients with tremor either due to PD or ET in whom DBS was successfully performed between 2009-2012 were included in the present study. The position of the stimulating electrodes (i.e. correlated with the best control on tremor) was calculated using postoperative CT co-registered with preoperative 3T T2-weighted MR (iPlan Net, Brainlab AG, Germany) and OPTIVISE software (Medtronic Inc., Minneapolis, USA). For each patient, the volume of tissue activated (VTA) was calculated. The Kruskal-Wallis/ Wilcoxon test were used for statistical analysis. A $p < 0.05$ was considered as statistically significant.

Results: The mean position of the STN stimulating contacts was (in mm) AP=-2.34, LAT=12.45, VERT=-2.76, whereas AP=-5.74, LAT=13.32, VERT= -1.95 for the Vim ($p < 0.05$). The mean radius of the VTA was 3.76mm. Although the 2 stimulation sites were significantly different in terms of AC-PC coordinates, the VTA co-registered with the preoperative image of each individual patient interestingly showed a stimulation site inferior to the Vim and superior in >80% of the cases

Conclusion: Although the stimulation site for tremor in PD or ET was found in 2 different points according to AC-PC coordinates, VTA analysis in each individual patient suggests that stimulation of these 2 sites may actually involve a unique structure. According to diffusion tensor imaging (DTI) studies, the dentatorubrothalamic tract (DRTT) is crossing this area could and may be the optimal point of stimulation. A prospective study is under investigation to confirm these findings

#241

Probabilistic tractography-based connectivity of the active contact region after Vim-DBS for Essential tremor

Péter Szloboda (1), István Valálik (1)

1. Department of Neurosurgery, St. John's Hospital, Budapest, Hungary

Introduction: The thalamus has been known as a notorious target of stereotactic surgery in case of various types of tremor since the middle of the 20th century. Presently, the mechanism of action and connectivity of the ventralis intermedius (Vim) and the ventralis oralis posterior (Vop) nuclei is still unidentified. The aims of the study are to determine anatomical location of the active contacts, mapping the active contact connectivity with tractography and work out a procedure for better individual target positioning.

Methods: Eleven consecutive patients with Essential tremor underwent Vim-DBS surgery. Stereotactic planning was performed with custom-developed Vister-3D software with stereotactic CT-to frameless MR image fusion. The target was defined on the AC-PC plane, 11,8-13,2 mm laterally from the midline and anteriorly from the PC 1-2 mm behind of 1/3 AC-PC distance. Model 3389 electrodes were implanted with RM or MHT stereotactic devices on 19 operated sides. Eight patients had bilateral and 3 patients had unilateral Vim-DBS with a mean follow-up of 18.3 ± 11.8 (3-43) months. The electrodes were connected to Kinetra or Activa SC/PC implantable pulse generators (Medtronic Inc). The clinical evaluation included the Fahn-Tholosa-Marin Rating Scale (FTM), whereas head and upper limb resting and postural tremor were captured with custom-developed infrared passive marker-based analyser of motions. The kinetic tremor was measured on digital spiral drawing test. The position of the clinically most effective and active contact(s) were located on preoperative MRI to-postoperative CT image fusion, with further registration to the MNI152 standard atlas-space. Then, we processed a probabilistic diffusion tractography with FMRIB Software Library.

Results: The tremor amplitude reduction reached 90% in all cases. In our investigation the motor thalamus determined by probabilistic classification did not contain the region of interest (ROI) of the active contacts. With the utilization of the Harvard-Oxford cortical structural atlas we have found two main connections of the ROI of the active contacts. The frontal projections of the ROI did not correspond to the motor and premotor connections of the thalamus. The connectivity to the supplementary motor cortical area and to the medial part of the superior frontal cortex seemed to play a key role in the efficient stimulation.

Conclusion: In our investigation the drawing connections are consistent with the published anatomical studies but we would like to reveal that the non-invasive DTI-tractography still needs some modifications to help us with the individual targeting of the Vim nucleus.

#256

Spinal cord stimulation improves gait performance in advanced parkinson disease in chronic STN-DBS patients: pilot study

Erich Talamoni Fonoff (1), Carolina Oliveira Souza (1), Carolina Pinto Souza-Pinto (1), Maria Gabriela Santos-Ghilardi (1), Rubens Gisbert Cury (1), William Omar Contreras-Lopez (1), Egberto Reis Barbosa (1), Manoel Jacobsen Teixeira (1)
 1. Division of Functional Neurosurgery, Department of Neurology, University of São Paulo Medical School, São Paulo, Brazil

Introduction: while STN-DBS improves the quality of life of patients by addressing the cardinal symptoms of PD and reducing levodopa-induced dyskinesias, benefits in postural instability and gait disturbance (PIGD) are modest and seem to fade away in long-term follow-up. PIGD can still be a problem even with optimized pharmacological therapy and DBS together. Data from animal PD model suggest that spinal cord stimulation (SCS) can enhance locomotion in mice. Although clinical results mostly from case reports in PD patients are still conflicting, a few patients benefited from SCS in thoracic levels. The aim of this report is to present the results of SCS of upper thoracic levels on gait in advanced PD patients in long term follow-up over after bilateral STN DBS.

Methods: Three advanced PD patients (age of 62,7y, 15,5y of PD, 5y after DBS in average) with primary symptoms and dyskinesias controlled by the combination of optimized oral medication and bilateral STN-DBS (Average UPDRS III ON-DBS/OFF-Med= 27,25), but still experiencing impaired locomotion due to moderate or severe PIGD. Patients received an implantable SCS system (16 channel paddle electrode) over the epidural space of upper levels of thoracic spinal cord. Clinical evaluation of gait was performed before and after the SCS implant and also ON/OFF trials after stimulation parameters were set. The stimulation parameters consisted in high frequency (300Hz), 90mcs and current just over the sensory threshold, ranging from 2.5 to 4.6 mA. The electrodes spatial conformation was tripolar (three columns 5-6-5) high enough of Gait evaluation consisted in Timed Up and GO test (TUG), 20-meter-walk test and Dual task Walking trial.

Results: High frequency spinal cord stimulation induced a modest additional improvement in UPDRS III of 14,9% and axial symptoms UPDRS sub score of 23,7% in average over DBS-ON MED-OFF condition. The most significant results were observed in gait. The TUG test revealed a decrease in number of steps by 58,4% and also a decrease in the time in walking trial by 61,3%. When The 20-meter walking revealed also improvement of 53,9% in the number of steps and decrease the time by 53,8% in average. The improvement in gait also included a increase in average step length from 30,5cm to 50,8cm. The average improvement in gait during dual task was a decrease in number of steps by 40,9% and in the time by 45,4%.

Conclusion: Although this is a pilot study with a limited number of patients, the data presented here in suggests that high frequency stimulation of the upper thoracic levels of spinal cord may improve considerably gait performance in advanced Parkinson disease in addition to STN-DBS. The present results contradict the results observed in SCS of the cervical spine and should be explored deeply in the future.

#271

Subthalamic spectral densities in Parkinson's disease and the effect of steering deep brain stimulation

LJ Bour, PhD¹, MAJ Lourens, PhD¹, R Verhagen, MSc¹, RMA de Bie, MD, PhD¹, P. van den Munckhof, MD, PhD², MF Contarino, MD, PhD^{1,3}, PR Schuurman, MD, PhD².

¹Department of Neurology and Clinical Neurophysiology, Academic Medical Center, University of Amsterdam, the Netherlands,

²Department of Neurosurgery, Academic Medical Center, University of Amsterdam, the Netherlands, ³Department of Neurology, Haga Teaching Hospital, The Hague, The Netherlands

Introduction: A new deep brain stimulation lead with a multidirectional 32-contact array has been tested during stereotactic surgery. Since contacts are pointing in different directions, in principle it is capable of directionally steering stimulation and to record local field potentials. The spatial and temporal content of these potentials, related to symptoms, could be used to determine how to direct the current delivered through a selection of the contact points.

Methods: Eight patients with Parkinson's disease are included in the study. After microelectrode recording the new 32-contact lead is temporarily inserted during surgery. The multidirectional 32-channel local field potential recordings are measured simultaneously at different depths and in different directions. Frequency analysis of the local field potentials is performed at baseline, just prior to and immediately after the stimulation period.

Results: The spatial distribution of power spectral densities of local field potentials across the contact array at baseline shows a clear relationship with the abnormal oscillatory behaviour of the parkinsonian STN. In addition, subthalamic local field potentials show a frequency dependent suppression/enhancement of the oscillatory activity in the 10-45 Hz frequency band after different modes of stimulation, including four different 'steering' and spherical mode. The amount of suppression/enhancement also depends on the direction of steering.

Conclusion: Through a new 32-contact deep brain stimulation lead it is possible to perform simultaneous subthalamic potentials recordings at different depths and in different directions without moving the electrode, providing multidirectional spatial and temporal information about disease-related subthalamic electrical activity and the effect of stimulation. The data provided may be of benefit in predicting how to steer the current in the most effective way.

#272

Deep brain stimulation: life-long treatment, life-long complications.

O. van der Veer¹, MD, L. Bour², PhD, R.M.A. de Bie³, MD PhD, P.R. Schuurman¹, MD PhD, P. van den Munckhof¹, MD PhD
Dept. of Neurosurgery¹ Academic Medical Center, Amsterdam, NL; Dept. of Neurophysiology² Academic Medical Center, Amsterdam, NL; Dept. of Neurology³ Academic Medical Center, Amsterdam, NL.

Objective: To evaluate infectious, haemorrhagic, and hardware-related complications of both initial deep brain stimulation (DBS) surgery and repeated internal pulse generator (IPG) and other hardware replacements in our DBS centre during the past 20 years.

Introduction: Numerous reports on DBS complications have been published thus far. However, the emphasis was almost exclusively on the initial implantation of hardware, and not on the complication encountered during the rest of a patient's 'DBS life'.

Methods: Since 2005, we prospectively monitor complications of DBS. For the period 1993 (when the first DBS case was operated in our centre) until 2005, we retrospectively analysed the clinical and operative records of all patients that underwent DBS in our centre.

Results: In the period 1993 to 2013 586 patients underwent DBS surgery at our centre. During this period, 762 IPG replacement surgeries were performed. 48 patients (8%) underwent repositioning of DBS electrodes (25 unilateral, 23 bilateral) because of suboptimal clinical effects: in 25 patients there was a post-operative displacement of the electrode(s) from their desired targets (19 upwards, 6 downwards), in 13 patients a new anatomic location was targeted in 10 patients the desired target was not reached in initial surgery. Infection and/or erosion of the hardware through the skin was the next most common complication: 45 patients (8%) required reoperation, usually consisting of removal of the infected/eroded part or, in some cases, all of the hardware on the affected side. In almost half of these cases the infection/skin erosion occurred more than 6 months after surgery, and often many years later (average after 3 years, with a maximum of 14 years). Hardware related discomfort requiring reoperation (7%) was the third most common complication. Twenty-four patients (4%) underwent reoperation due to hardware malfunction. Thirteen patients (2%) underwent a reoperation due to subcutaneous haemorrhage after IPG (re)placement. Ten patients (2%) developed a symptomatic intracranial haemorrhage as a direct result of electrode implantation. Of these, 6 patients showed complete neurological recovery. One hundred and four patients experienced one complication, and 15 patients experienced two or more complications. Four hundred and sixty-seven patients (80%) experienced no complications at all during their DBS life.

Conclusion: Although rates of all individually occurring complications are relatively low, both patients and DBS surgeons should realize that DBS is a life-long treatment and that complications can occur throughout this period. One out of five DBS patients will encounter a complication requiring reoperation.

1.1.2 Psychiatric Disorders

#90

Deep Brain Stimulation for Treatment Resistant Major Depression – Targeting the Dysfunctional Human Reward System

Volker Coenen (1)

1. Stereotactic Neurosurgery, University Hospital Freiburg, Freiburg, Germany

Introduction: A core symptom of major depression is anhedonia (decreased drive and reward for pleasurable activities) and reduced motivation. The human reward system consists of the neural pathways involved in eliciting rewarding experiences in animals and humans; its structures, the striatum (particularly the ventral striatum or nucleus accumbens (NAcc) and the medial forebrain bundle (MFB), are important in emotional memory, and might mediate those symptoms. Antidepressant effects of Deep Brain Stimulation (DBS) to the NAcc and two additional targets have been systematically assessed and results in response in 50-60% of patients studied, albeit only at relatively high stimulation intensities. Using probabilistic diffusion tensor imaging (DTI) we were able to demonstrate that all stimulation sites stimulate fibers of the MFB and hypothesized that DBS to the MFB closer to its origin in the ventral tegmental area might be associated with higher antidepressant efficacy at lower stimulation intensities since the extent of antianhedonic effect might be related to the recruited amount of fibers of the MFB. Recently we demonstrated unexpectedly rapid effects of this procedure.

Methods: Study 1: Eight patients suffering from extremely treatment resistant forms of major depression underwent implantation of DBS electrodes at the MFB after individualized targeting using probabilistic DTI.

Study 2: 16 patients with the same criteria as those in study 1 were randomized in to either re-receiving MFB-DTI immediately after implantation or after two months of sham stimulation.

Results:

Study 1: As previously published, seven of eight patients showed rapid improvement within 5 days of stimulation at intensities of about 30% of the ones used in previous studies. Here we re-report on outcomes after one year of therapy. The whole group responded with a 57.9% improvement in depressive symptomatology as rated with the MADRS. Six patients were classified as responders.

Study 2: At the time of submission (June 2014) 12 of the 16 patients were implanted. So far, all subjects showed acute improvement in depressive symptomatology after onset of real DBS stimulation, in parallel to the ones included in study 1. At the time of submission, most patients were classified as responders. In the symposium, six months stimulation data of all patients will be presented.

Conclusion: Taken together, results from both studies point to the fact that DBS to the MFB is associated with high antidepressant efficacy in very treatment resistant patients with a rapid on-set. The MFB seems to be a germane structure within a network of centers processing affective stimuli. The unexpected acute onset of antidepressant action challenges current hypotheses on network dysfunctions putatively involved in major depression.

#136

Anterior Cingulotomy for Refractory Major Depression: case series outcomes and predicting response.

Serenella Tolomeo (1), David Christmas (1), Muftah S. Eljamel (1), J. Douglas Steele (1), Keith Matthews (1)
1. Division of Neuroscience, University of Dundee, Dundee, United Kingdom

Introduction: Anterior Cingulotomy (ACING) is an established neurosurgical treatment for patients with chronic pain, refractory Obsessive Compulsive Disorder (OCD) and treatment-refractory depression (TRD). However, it is not currently possible to predict the likelihood of response to surgery without exposing an individual patient to an experimental trial of neurosurgery. Therefore, developing methods to identify accurately responders and non-responders at an individual level and prior to therapeutic intervention is an important clinical challenge.

Methods: The present study reports the clinical outcomes (symptom burden – e.g. MADRS, HDRS17, HAD-A; functional measures; quality of life and neuropsychological performance) in a prospective case series of 20 consecutive patients with chronic, highly treatment refractory depression (TRD) who received ACING between 2001 and 2011. Clinical assessments were completed at baseline and at 12m follow-up. The degree of treatment-resistance was graded using MGH and Thase & Rush staging, plus ATHF scores. We predicted outcomes using discriminant analysis with 'leave-one-out' cross-validation.

Results: Ten patients (50%) met criteria for response (defined as > 50% reduction in baseline MADRS score) and ten (50%) were non-responders at 12m. Baseline MADRS score alone predicted outcome with 83% accuracy (responders 'vs' non responders). Those with highest baseline scores (MADRS >40) tended not to respond. Comparing responders and non-responders, the groups differed significantly [$p=0.02$] in terms of baseline MADRS scores. Measures of treatment resistance did not predict treatment outcome. There were no deaths and no suicides. One individual experienced asymptomatic haemorrhage (detected on scan) without any apparent sequelae. One patient experienced a single post-operative seizure, but required no continuing treatment.

Comprehensive neuropsychological assessment revealed no significant changes in the majority of tests of memory, executive functioning and intelligence. Neuropsychological performance tended to improve in ACING responders.

We have explored the relationships between clinical response and lesion characteristics. We now propose an optimal lesion topography that is associated with greatest clinical benefit.

Conclusion: In this single centre case series, the response rate to ACING for patients with chronic highly treatment refractory depression was 50%. There were few physical adverse effects and neuropsychological functioning was not impaired. Baseline MADRS scores could be used to predict clinical outcome at 12m with high accuracy. However, measures of treatment resistance could not be used to predict outcome.

#175

Delineation of the nucleus accumbens: targeting for deep brain stimulation

Laura Cif (1), Jocelyne Bloch (1), Etienne Pralong (1), Bogdan Draganski (2)

1. Département des Neurosciences Cliniques, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

2. Département des Neurosciences Cliniques; Laboratoire de Recherche en Neuroimagerie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Introduction: Despite increasing interest for the nucleus accumbens (NAc) neuromodulation in several psychiatric disorders (obsessive compulsive disorders, major depression, addiction and anorexia nervosa), there is a lack of consensual information about its delineation, functional anatomy and the site of the DBS target, as provided by anatomical and imaging studies. Reported radiological anatomy does not account for specific protocols allowing sharp delineation of the NAc from the other components of the ventral striatum and, for further functional subdivisions. We propose the use of high-resolution maps of magnetization transfer saturation for identification and delineation of the NAc, voxel based morphometry (VBM) to determine its dimensions and probabilistic tractography to examine the in vivo connectivity of the nucleus. Our hypothesis is that NAc's pattern of connectivity could guide DBS target location, in relation with its functional divisions.

Methods: To delineate and provide the connectivity pattern of the NAc, we acquired images in 11 healthy subjects (6 females) on a 3T whole body MR system (Magnetom Prisma, Siemens Healthcare, Erlangen, Germany). We used a quantitative structural MRI comprising a multi-parameter mapping protocol of whole-head 3D multi-echo fast low angle shot (FLASH) datasets with T1-, PD-, and MT-weighting at 1 mm isotropic resolution and diffusion weighted imaging (DWI) of single-shot echo-planar imaging (EPI) of 1.5mm isotropic resolution and whole-brain coverage (high $b=1000$ s.mm⁻² along 61 directions, and 7 directions at a low b -value of 0 s.mm⁻²). DTI preprocessing were performed using the Artefact correction in diffusion MRI (ACID) into the batch system of Statistical Parametric 8 (SPM8) for eddy current and subject motion effects, and using the FMRIB Software Library (FSL) (version 5.0.1): segregation of brain tissue from non-brain tissue, local fitting of diffusion tensors and construction of individual FA maps using DTIFIT from FMRIB's Diffusion Toolbox and visualization of the results prior to tensor estimation in BEDPOSTX. Seed and target maps were created in subject-specific native space for automated segmentation and structure labeling with FSL, Individual Brain Atlases using SPM (IBMASPM) and Freesurfer. Probabilistic tracking with crossing fibers was performed. All fiber tracts were obtained through a two-ROI approach (seed ROI and seed to target ROI).

Path Distribution Estimation: Seed ROI Registration from structural to diffusion space was performed using FMRIB's Linear Image Registration Tool (FLIRT) in FSL. After applying BEDPOSTX, connectivity distribution from the specified region of interest was obtained by running tractography analyses using probtrackx (FSL) and the segmented left and right accumbens seeds and the output matrix from the registration. We analyzed the NAc's targets and identified them using 2D and 3D images to aid the interpretation of the results. Connectivity-based Seed Classification: ProbTrack allowed classifying all the voxels within the NAc's mask by sites they are connected with.

Results: The mean \pm standard deviation of the left and right segmented volumes of the accumbens are 508.7 ± 127.9 mm³ and 367 ± 85.9 mm³ respectively (p -value = 0.013). We identified the following cortical and subcortical structures as being connected with NAc: anterior cingulate, medial orbital cortex, frontal superior, mid frontal gyrus, temporal inferior gyrus, middle temporal gyrus, temporal superior gyrus, posterior cingulum, angularis gyrus, cuneus, fusiformis gyrus, insula, lingual gyrus, hippocampus, parahippocampal gyrus, rectus gyrus, as cortical targets and the caudate nucleus, putamen, amygdala, pallidum, putamen, subthalamic nucleus, substantia nigra, thalamus as subcortical targets. We observed differences in the pattern of connectivity between the left and right NAc.

Conclusion: NAc delineation can be improved by the use of new protocols that allow an increased contrast at the level of the basal ganglia. Significant inter-individual variations are measured for the volume and the pattern of connectivity of NAc, which should orientate towards the identification of the surgical target on an individual basis and direct targeting using multiparametric maps and probabilistic tractography.

#273

DEEP BRAIN STIMULATION IN NUCLEUS ACCUMBENS / VENTRAL ANTERIOR LIMB OF THE INTERNAL CAPSULE IS EFFECTIVE IN DECREASING DEPRESSIVE SYMPTOMS

I.O. Bergfeld, M.H. Mantione, P. van den Munckhof, P.R. Schuurman, D. Denys

Introduction: Major Depressive Disorder (MDD) is a highly prevalent psychiatric disorder with an estimated lifetime prevalence of 14.6% across high-income countries. As many as 30% of MDD patients do not respond sufficiently to consecutive treatment alternatives and suffer from therapy-resistant depression (TRD). Preliminary studies show Deep Brain Stimulation (DBS) of several brain areas (e.g. Subcallosal Gyrus, Ventral Capsule / Ventral Striatum, Nucleus Accumbens) to be a promising treatment for these patients. Here, we assessed the efficacy and tolerability of DBS targeted at the Nucleus Accumbens / ventral Anterior Limb of the Internal Capsule (NAc/vALIC).

Methods: In an ongoing study we have included 20 TRD patients, who underwent bilateral deep brain stimulation targeted at the NAc/vALIC. Following surgery, patients entered an open 12-month optimization phase. We assessed patients before surgery and following the optimization phase with the Hamilton Depression Rating Scale (HDRS), a semi-structured 17-item interview to assess depressive symptoms (range: 0-52). Primary outcome measure was the percentage responders, based on a $\geq 50\%$ decrease on the HDRS at the end of the optimization phase relative to baseline.

Results: We classified 8 out of 20 patients (40.0%) as responders and 12 of 20 patients as non-responders (60.0%) following DBS optimization. On average, the responders decreased 70.3% (SD: 13.7%) on the HDRS, whereas 12 non-responders increased 20.6% (SD: 33.4%). In 2 patients a mild and permanent adverse event was recorded (pollakiuria). All other adverse events were transient.

Conclusion: NAc DBS is effective in 40% of the patients and was generally well tolerated. In future studies placebo effects should be ruled out in a randomized sham / active study.

#274

DTI/Tractography of the Human Nucleus Accumbens – implications for psychosurgery.

Neto L^{1,2}, Sousa J⁴, Reimão S², Campos J², Nunes R⁴, Gonçalves-Ferreira A^{1,3}

1- Anatomy Department, Lisbon Medical School, Portugal.

2- Neuroradiology Department, Lisbon North Medical Center - Santa Maria University Hospital, Lisbon, Portugal.

3- Neurosurgery Department, Lisbon North Medical Center - Santa Maria University Hospital, Lisbon, Portugal.

4- Institute of Biophysics and Biomedical Engineering, Faculty of Sciences, University of Lisbon, Portugal.

Introduction: The Human Nucleus Accumbens (Acc) has become an important target for deep brain stimulation (DBS) in refractory neuropsychiatric disorders such as Obsessive-Compulsive Disorder and addiction. In animals, the Acc is divided in a ventromedial shell, associated with the limbic system and a central core, related to the motor system. This dichotomy is not however clearly seen in humans. Previous studies performed by our group, in cadavers, established the 3D-stereotactic anatomy of the nucleus and revealed a subcommissural extension of the Acc, which could correspond to the shell described in the rat. Now it is our purpose to perform a characterization of the Acc *in vivo*, using high-field MRI and Diffusion-Tensor-Imaging/Tractography. We also apply this technique to segment the nucleus into a core and shell division, given the importance of the exact identification of targets in psychosurgery.

Methods: T1-weighted 3TMR images were acquired in 10 healthy volunteers and 32-direction DTI was obtained. Seed masks for the Acc were generated using FreeSurfer and probabilistic tractography was performed using FSL. The probability of connectivity between seed voxels and several brain areas was determined and subjected to k-means clustering analysis in order to define 2 regions.

Results: On MRI the Acc could be segmented into two distinct regions in all cases. The preferential connectivity between these 2 regions and other brain areas is presented and its correlation to the previous post-mortem studies is established.

Conclusions: Advanced MRI techniques allow the *in vivo* segmentation of the human Acc and represent an additional and useful tool in the precise and safe target definition for DBS.

1.1.3 Epilepsy

#46

DEEP BRAIN STIMULATION OF THE CENTROMEDIAN THALAMIC NUCLEUS: A SINGLE BLIND TRIAL

Cristina Torres (1), Jesus Pastor (2), Marta Navas (1), Eduardo García-Navarrete (1), Paloma Pulido (1), Lorena Vega-Zelaya (2), Oscar Garnés-Camarena (2), Rafael Sola (1)

1. Neurosurgery, Hospital La Princesa, Madrid, Spain

2. Clinical Neurophysiology, Hospital La Princesa, Madrid, Spain

Introduction: Deep Brain Stimulation (DBS) of the thalamus is an emerging treatment for medically refractory epilepsy patients, who are resistant or not suitable for resective surgery. The aim of this study is to evaluate the efficacy of DBS for intractable epilepsy with a controlled single blind trial.

Methods: Patients were assessed according to our Epilepsy Surgery Unit preoperative protocol, and diagnosed with generalized epilepsy. Bilateral DBS electrodes were stereotactically inserted, with electrophysiologic confirmation of their position. The baseline pre-implantation period was followed by a control period consisting in a blind stimulation-OFF phase of three months, a three months blind stimulation-ON phase, and a six months unblind stimulation-ON phase. The control period was followed by an unblind long-term extension phase with stimulation-ON.

Results: Six patients were included in the study. Mean age at surgery was $30,8 \pm 6,8$ years, and mean age at epilepsy onset was $7,8 \pm 2,1$. All but one patients had >50% improvement in seizure frequency during the blind period and in the long-term extension phase (mean follow-up $13,5 \pm 9,3$). Among these 5 patients, three had 67-80% reduction in seizure frequency. Other effects such as reduction in seizure severity or an improvement in the level of alertness were reported by four patients. One patient experienced an increase in seizure severity with stimulation.

Conclusion: Stimulation of CMN yielded a >50% seizure frequency reduction in five out of our six patients with intractable generalized epilepsy. DBS of CMN should be considered as a treatment option particularly in patients with refractory generalized epilepsy syndromes.

#57

Defining anterior nucleus of thalamus (ANT) as a surgical target in epilepsy: delineation using 3T MRI and intraoperative microrecording

Timo Möttönen (1), Jani Katisko (2), Joonas Haapasalo (1), Timo Tähtinen (1), Tommi Kiekara (3), Veikko Kähärä (3), Jukka Peltola (1), Juha Öhman (1), Kai Lehtimäki (1)

1. Department of Neurosciences and Rehabilitation, Tampere University Hospital, Tampere, Finland

2. Neurosurgical Research Unit, Oulu University Hospital, Oulu, Finland

3. Department of Radiology, Tampere University Hospital, Tampere, Finland

Introduction: Deep brain stimulation (DBS) is a minimally invasive method to treat an increasing number of neurological and psychiatric disorders, including epilepsy. Targeting poorly defined deep structures is based in large degree on stereotactic atlas information, which may be a major source of inconsistent treatment effects.

In the present study, we aimed to study whether a recently approved target for epilepsy (anterior nucleus of thalamus, ANT) is visualized in clinically established 3T MRI and whether ANT is delineated using intraoperative microelectrode recording (MER). We have especially focused on individual variation in the location of ANT in stereotactic space. We also aimed to demonstrate the role of individual variation in interpretation of MER data by projecting samples to AC-PC and ANT-normalized coordinate systems.

Methods: Detailed analysis of ANT delineations in 3T MRI short tau inversion recovery (STIR) images from eight patients undergoing DBS for refractory epilepsy was performed. Coronal and sagittal cross-sectional models of ANT were plotted in AC-PC coordinate system to study individual variation. A total of 186 MER samples collected from 10 DBS trajectories were analyzed, and the location of each sample was calculated and corrected accordingly to location of final DBS electrode and projected to the AC-PC based and ANT-normalized coordinate system.

Results: Most of the key structures in the anatomic atlas around ANT (mamillo-thalamic tract and internal medullary lamina) were identified in STIR images allowing visual delineation of ANT. We observed a high degree of anatomical variation in the location of ANT, and the cross-sectional areas overlapped by study patients decreased in a linear fashion with increasing number of patients. MER information from 10 individual trajectories correlated with STIR signal characteristics by demonstrating a spike negative zone, presumably white matter layer, at the lateral aspect of ANT in ANT-normalized coordinate system as predicted by STIR images. However, MER information projected to AC-PC coordinate system was not able to delineate ANT.

Conclusion: ANT is delineated in 3T MRI by visualization of a thin white matter layer lamina between ANT and other nuclear groups that lacks spiking activity. Direct targeting in the anterior thalamic area is superior to indirect targeting due to extensive individual variation in the location of ANT. Without detailed imaging information, however, a single trajectory MER has little localizing value.

#108

Amygdalo-hippocampotomy: long-term (5 years) epilepsy outcome

Antonio Gonçalves-Ferreira (1), Alexandre Rainha-Campos (1), Manuel Herculano Carvalho (1), Carlos Morgado (2), Carla Bentes (3), Rita Peralta (3), Jose Pimentel (3)

1. Neurosurgery, University Hospital Santa Maria, Lisbon, Portugal

2. Neurological Imaging, University Hospital Santa Maria, Lisbon, Portugal

3. Neurology, University Hospital Santa Maria, Lisbon, Portugal

Introduction: Since 2007 we performed selective amygdalo-hippocampotomy, with hippocampal disconnection instead of removal, for refractory temporal lobe epilepsy (TLE) due to mesial temporal lobe sclerosis, in order to decrease vascular and cranial nerve dissection risk and save time. The early results were equivalent to patients submitted to amygdalo-hippocampectomy. Now we comparatively review the results after 5 years.

Methods: 27 MTLs patients (16 females) aged 20-59 years (mean:40y) were operated with this technique: selective ablation of lateral amygdala plus peri-hippocampal disconnection, including the para-hippocampal gyrus. In 20 patients the results were evaluated at 2 years post-operation. Now 18 patients were re-evaluated at 5 years post-operation and the results compared with those and with 126 patients submitted to hippocampectomy.

Results: Outcome for epilepsy: good/very good in 19/20 patients (95%) after 2 years reduced to 15/18 patients (83.3%) after 5 years, with Engel Class I in 12 (66,6%) and Class II in 3 (16,7%); bad in 1/20 patients (5%) at 2 years, moved to 3/18 patients (16,7%) at 5 years (Class III in 2, Class IV in 1). These features are equivalent to those submitted to hippocampectomy.

Conclusion: Amygdalohippocampotomy at 5 years post-operation revealed to be as effective as amygdalohippocampectomy, both with less good results than at 2 years.

#133

Temporal resection is an effective treatment in patients with MRI negative intractable epilepsy

JB Cheserem (1), I Ughrardar (1), Irfan Malik (1), Antonio Valentin (2), Robert Elwes (2), Nandini Mullatti (2), Gonzalo Alarcon (3), Richard Selway (1)

1. Neurosurgery, Kings College Hospital, London, United Kingdom

2. Neurophysiology, Kings College Hospital, London, United Kingdom

3. Clinical neurophysiology, Kings College London, London, United Kingdom

Introduction: Anterior temporal lobectomy is an established treatment for epilepsy in patients with temporal abnormalities on MRI. It is often considered that patients with normal MRIs have a much lower chance of an excellent seizure outcome following surgery and the decision as to which patients should be proposed for surgical investigation remains controversial. We undertook a retrospective review of all our temporal resections for epilepsy and compared the outcome of those with normal MRIs with lesional cases.

Methods: Retrospective review of all temporal resections undertaken at a single institution between 1999-2014. We reviewed patient outcomes using the Engel classification and histology of patients with normal MRIs compared to those with congruent temporal lesions on MRI.

Results: A total of 211 temporal lobectomies were undertaken with 26 (12.3%) patients having normal MRI and 185 having congruent lesions on scans. Mean post-operative follow-up was 38 months (0-134). Patients with a normal scan had an average age of 33 years (22-54) at surgery with an average age of 15.5 years (2-38) at the onset of epilepsy. In patients with MRI positive findings the average age at surgery was 35 years (2-74) with onset of epilepsy at 14 years (0-62). All patients in both groups underwent a detailed epilepsy surgery assessment. Those with normal scans and some of those with discordant clinical features had intracranial electrode monitoring prior to resection.

Amongst patients with normal MRIs 19/26 (73%) patients had good outcome (Engel classification I or II), compared to 124/185 (77%) in the MRI positive group (P =not significant). Of those with normal MRIs the histology of 12/26 (43%) was consistent with mesial temporal sclerosis (MTS) and 11/26 (42%) were non-specific or normal. Histology from patients with lesions on MRI were 89/185 (48%) MTS, 37 (20%) tumours, 9 AVMs, 6 focal cortical dysplasias, 4 gliotic changes and 3 infarcts. Tumour cases consisted of 15 DNET, 13 gliomas, 3 meningiomas, 5 gangliomas and 1 tuberous sclerosis.

Conclusion: The presence of normal MRI neuro-imaging should not deter investigation with a view to epilepsy surgery. The outcome of those with temporal epilepsy is equally good with or without a focal MRI abnormality.

#165

Prospective evaluation of Gamma Knife Surgery in Hypothalamic Hamartomas : about a series of 57 patients.

Jean Regis (1), Medhi Lagmari (1), Géraldine Daquin (2), Nathalie Villeneuve (3), Fabrice Bartolomei (4), Patrick Chauvel (4)

1. *Functional Neurosurgery, Aix Marseille University, Marseille, France*

2. *Epileptology, Hôpital Henri Gastaut, Marseille, France*

3. *Epileptology, Hopital Henri Gastaut, Marseille, France*

4. *Epileptology, Aix Marseille University, Marseille, France*

Introduction: Epilepsies associated to Hypothalamic Hamartomas are frequently drugresistant with a severe psychiatric and cognitive comorbidity. We have organized a prospective trial in order to evaluate the safety efficacy of radiosurgery using the Gamma Knife.

Methods: Between October 1999 and October 2007, 57 patients have been investigated, included and treated by Gamma Knife in Timone University Hospital. Preoperative work-up and 3 years evaluation were including: Seizure diary, Neuropsychological testing, Psychiatric evaluation, endocrinological evaluation, visual field and acuity. Till now, follow up of more than 3 years is available for 48 patients. The hamartomas were of topological type I in 11 pts, Type II in 15 pts, Type III in 17 pts, Type IV in 1pt, Type V in 1 pt and mixte Type in 2 pts. The median of the marginal dose was 17 Gy (min 14 max 25Gy). The median of the volume was 398 mm³ (28 – 1600). 28 pts (58,3%) have been treated twice due to partial result.

Results: The median follow up was 21 months (25-107). At last follow up the rate of Engel I was 29,2 %, Engel II 33,3% (I+II 62,5%) & Engel III (20%). Global Psychiatric and Cognitive comorbidity was considered cured in 28%, improved 56%, stable 8% and have continue to worsen in 8%. No permanent neurological (specialy no mnesic deficit) side effect is reported. A non disabling transient poikilothermia was observed in 3 patients (6,2 %). A transient increase of seizure frequency is reported in 8 pts (16,6%). Microsurgery was proposed due to insufficient efficacy of GKS in 7pts (14,5%) (postop Engell 50%).

Conclusion: This prospective trial is demonstrating the very good safety efficacy of Gamma Knife radiosurgery in the long term. Beyond seizure reduction, the improvement of the psychiatric, cognitive condition and school and social inserion is turning out to be the major benefit of GKS in this frequently catastrophic epilepsy group.

#166

Gamma knife radiosurgical treatment of paracentral epilepsy

Jean Regis (1), Aileen McGonigal (2), Fabrice Bartolomei (3)

1. *Functional Neurosurgery, Aix Marseille University, Marseille, France*

2. *Epileptology, Aix Marseille University, Marseille, Finland*

3. *Epileptology, Aix Marseille University, Marseille, France*

Introduction: In pharmacoresistant focal epilepsies involving the central region, risk of motor deficit generally contraindicates cortical resection. Gamma knife radiosurgery (GK) is an established treatment for certain focal epilepsies, notably mesial temporal epilepsy and epilepsy associated with hypothalamic hamartoma. However the safety profile and efficacy of GK in motor cortex epilepsies has not previously been demonstrated.

Methods: We report 4 patients (18-31 years) with focal sensorimotor epilepsy seizures arising from the paracentral lobule, demonstrated by stereoelectroencephalography (SEEG).

Results: Two patients had undergone prior cortical resection involving paramedian premotor regions. A marginal dose of 24 Gy was delivered to a focal zone involving paracentral lobule. Volume of treatment in the 4 patients ranged from 1.6cm³ to 3.18 cm³ (mean 2.33, median 2.34). No motor deficit or other adverse affect occurred. Follow up was available for at least 3 years (range 36-78 months; median 49). On patient was unchanged; another had temporary improved seizure control but subsequent relapse; and 2 patients achieved Engel's Class 1B outcome. Both improved patients had gradual disappearance of objective motor ictal semiology (6-12 months post-GK), preceding reduced seizure frequency (12-18 months onwards). Cerebral MRI showed no significant change during the follow-up period.

Conclusion: GK is a potentially useful treatment for focal paracentral epilepsies, where conventional surgery would carry unacceptable risk of motor deficit.

#170

Application of stereotactic 3D photographic texture-encoded surface contour imaging in epilepsy surgery

David Roberts (1), Xiaoyao Fan (1), Songbai Ji (1), Alex Hartov (1), Keith Paulsen (1)
 1. Neurosurgery, Dartmouth, Lebanon, United States

Introduction: This study describes the implementation of an enhanced stereoptic-based imaging system and in a series of epilepsy surgeries explores the hypothesis that intraoperative stereotactic co-registration of three-dimensional contour optical imaging of the surgical field with conventional radiologic imaging modalities will enable localization guidance (cortical, electrode, mapping and resection), updated registration, and archival documentation.

Methods: An upgraded stereovision system comprised of two 1024 X 768 color CCD cameras attached to an operating microscope at a binocular port and employing an optical flow algorithm provides 3-D coordinate localization of each pixel at a frame rate of 15/sec. Accuracy of the current implementation of this system was assessed in phantom and during surgery by feature localization relative to a tracked stylus. Surgical field localization with respect to preoperative MRI, utility in functional mapping, displacement mapping of cortical features and of implanted electrodes, and intraoperatively updated registration were performed.

Results: Accuracy assessment by feature localization relative to a tracked stylus was 1.0 ± 0.5 mm. Application in 155 epilepsy and tumor cases superposed high resolution, surface-contour color images on MRI 3-D reconstructions, and in 34 epilepsy cases these were used for intraoperative planning, localization, guidance, and documentation. Displacement fields enabled intraoperative updated registration from initial errors of 4.0 - 9.8 mm. In eight patients undergoing two-stage procedures, the mean average displacement of subdural electrodes at second surgery was 5.2 ± 1.8 mm, with a range of 0.6 to 12.9 mm.

Conclusion: A stereovision-based imaging system integrated into the operating microscope can be efficiently incorporated into the work-flow of the surgical procedure. Intracranial electrode and cortical mapping localization, updated correlation with MRI, and documentation through stereotactically-registered 3-D optical images were demonstrated to be feasible, accurate, efficient, and useful in epilepsy cases.

1.1.4 Pain

#31

Impact of deep brain stimulation on visceral pain in a rat model.

Pierre HANNEQUIN (1), Mathieu MELEINE (2), Pierre DECHELOTTE (2), Guillaume GOURCEROL (3), Stéphane DERREY (1)
 1. Neurosurgery Department. Nutrition, Gut & Brain Unit (INSERM U1073), Institute for Biomedical Research and innovation, CHU ROUEN, ROUEN, France
 2. Nutrition, Gut & Brain Unit (INSERM U1073), Institute for Biomedical Research and innovation, Université de Rouen, ROUEN, France
 3. Department of Physiology, Rouen University Hospital. Nutrition, Gut & Brain Unit (INSERM U1073), Institute for Biomedical Research and innovation, Rouen, Rouen, France., CHU ROUEN, ROUEN, France

Submitter: Mr HANNEQUIN Pierre (FR)

Introduction: The modulation of somatic and neuropathic pain intensity by deep brain stimulation is well documented in the literature. But, to our knowledge, the impact of deep brain stimulation on visceral pain has never been investigated before. The aim of this experimental work was to assess whether central nervous system modulation may impact on intensity of pain in a model of rats affected by an acute visceral pain.

Methods: In anaesthetized rat, following the implantation of unilateral depth microelectrode under stereotactic conditions, the colonic sensitivity was monitored by measuring blood pressure (BP) variation as pseudo-affective reflex to the colonic distension obtained by a balloon connected to an electronic barostat. Rats were divided in five groups related to the stimulated target: ventro-postero-lateral (VPL) thalamus (n=20), posterior insula (n=10), locus coeruleus (n=8), subthalamic nucleus (STN) (n=8) and cingular (n=8) groups. Variation of BP was quantified after isobaric graded CD and compared in off-stimulation and on-stimulation (rectangular pulses of 120 mAmp delivered at a frequency of 100 Hz and impulse duration of 60 μ s). After animal euthanasia, the location of the tip of microelectrode within the target was checked using cresyl-violet staining and c-fos protein expression was quantified by immuno-staining in region of interest.

Results: For a 80 mm Hg colonic distension threshold, the stimulation (on-period) of the VPL nucleus induced a significant decrease on BP compared to the off-period. In this group, the difference was respectively 1,78 mmHg ($p<0,05$) and 2,78 mmHg ($p<0,001$) for the subgroups evaluated in off/on/off (n=10) and in off/off/on (n=10). No group effect was observed for VPL. No statistical difference was observed for the STN, insular, cingular and locus coeruleus target between the off and on-periods.

Conclusion: Unilateral VPL stimulation impacts on visceral sensitivity in anesthetized rats with a significant decrease of the intensity of pain in response to colonic distension. On visceral pain this effect has never been demonstrated before in the literature.

#58

Possible reason for the loss of effectivity of motor cortex stimulation for treatment of neuropathic pain syndromes

wilhelm eisner (1), thomas fiegele (1), florian sohm (1)
 1. neurosurgical, medical university innsbruck, austria, innsbruck, Austria

Submitter: Mr Eisner Wilhelm (AT)

Introduction: Over 300 cases reported in the medical literature since 1991 indicate that Motor Cortex Stimulation (MCS) using 4 or more contact electrode paddles is effective for the treatment of neuropathic pain, in particular for central post-stroke pain (CPSP) and trigeminal neuropathic pain (TGN) /facial pain.

Methods: We experienced in 8 patients a reduction in effectivity of treatment after two years of treatment resulting in discontinuing of that treatment in our country. Some patient could live with the reduction in surgical pain therapy because they had a stable amount of pain reduction after two years of treatment and some therapeutic effect but reduced in all possible settings compared to the first year of treatment. The therapeutic effect got reduced slowly following a stable period of effectivity of 18 months. In three patients the therapeutic effect was reduced tramatically. We offered our patients DBS for neuropathic pain therapy. One patient wanted the stimulator which was almost empty to be removed and for the moment no further therapy. Two patients had such a worsened situation that they were "willing to suicide". We offered DBS, for which a stereotactic planning MRI was necessary. We had to remove the epidural electrode and stimulator system because our radiologists refused to perform a MRI with implanted neuromodulation devices. We removed the systems including recraniotomy of the patients.

Results: After removing the resume round electrode with eight contacts we found a scare tissue between dura and electrode in two patients. After removing the scare tissue we discovered in one patient a plate of calcified tissue. Now we knew why we had no positive stimulation effects anymore despite of full integrity of the stimulation system proven by regular thresholds of the electrode and the extension cables including the stimulator. In the first two years after the implantation of the system we could induce a cramp in the hand and face by current higher than 5.5 V. The other patient who wanted no other treatment for the moment was giving us the hint that the loss of effectivity of tretment has the same reason. Because the patient induced our one and only epileptic seizure during the test trial, after implantation of the electrode, with an extern stimulator. Instead of shutting down the stimulator he turned the intensity wheel to maximum power. After reduction of the therapeutic effect we could not provoke epileptic activity not even with the highest gain settings?

Conclusion: Epidural motor cortex stimulation seams to be temporarily effective to treat neuropathic pain. Patients with neuropathic pain should be informed preoperative of a possible limited therapeutic effectivity.

Comment: We remember that in the seventies electrotherapy was utilized for difficult fractures in sportsmen with a better calcification of the fracture. Additionally we had in a few patients with surgical spinal chord stimulation electrodes spinal stenosis in the area of the electrode due to calcification? We did not have these findings in percutaneous electrodes and DBS electrodes for more than 25 years and in many thousand patients.

#64

A tractography analysis of a new target of Deep Brain Stimulation for pain: the Anterior Cingulate Cortex

Sandra Boccard-Binet (1), Saad Jbabdi (1), Tim Van Hartevelt (2), Morten Kringelbach (2), Henrique Fernandes (2), James FitzGerald (3), Erlick Pereira (3), Liz Moir (4), Alex Green (3), Tipu Aziz (3)

1. Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

2. Department of Psychiatry, University of Oxford, Oxford, United Kingdom

3. Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom

4. Oxford University Hospitals NHS Trust, University of Oxford, Oxford, United Kingdom

Submitter: Mme Boccard-Binet Sandra (GB)

Introduction: Pain is a multifaceted sensation with three dimensions: sensory (pain intensity), affective (pain unpleasantness) and cognitive (Melzack 1999). As described in a recent case series (Boccard, Pereira et al. 2012), Deep Brain Stimulation (DBS) targeting the sensory component has been utilised with various degrees of success. We recently demonstrated that some patients benefit from targeting brain areas of the affective dimension such as the anterior cingulate cortex (ACC) (Boccard, Neurosurgery, June 2014)(Boccard, Pereira et al. 2014). However, for some, DBS of the ACC failed.

Diffusion Tensor Imaging (DTI) is a magnetic resonance imaging based on the anisotropy of water molecule diffusion along neurons (Basser, Mattiello et al. 1994). The main diffusion direction corresponds to the predominant direction in oriented fibre bundles (Beaulieu and Allen 1994). Modelling the local diffusion permits estimation of these directions and to follow them with probabilistic tractography (Behrens, Johansen-Berg et al. 2003). It can be used to map tracts from given 'seeds' or Region Of Interest (ROI) such as the active contacts of electrodes (Behrens, Woolrich et al. 2003; Hyam, Owen et al. 2012).

Methods: We analysed the specific connectivity patterns of 7 chronic pain patients with DBS of the ACC to explain differences in treatment efficacy. One patient was pain free, 4 had partial pain relief and 2 did not feel any pain relief. Probabilistic tractography was performed by attributing each voxel a value representing connectivity between the seed (electrode contact) and the regions of interest (anterior and posterior cingulate cortex).

We found that the connectivity pattern from the electrode contacts to the ACC and to the PCC was statistically significantly greater in the brains of patients with little or no pain relief. Moreover, the connectivity to the PCC in the pain-free patient was much reduced compared to those with less pain relief.

Results: These data could indicate that DBS of the ACC is less effective for pain relief when choosing a region with connectivity to the PCC. Even though the ACC is thought to be the part of the CC involved in pain, elicited nociceptive messages reach the PCC first (Bromm 2004). We speculate that, in those non-responders to DBS of the ACC, the extra activity in the PCC may amplify nociceptive signals travelling from the PCC to the ACC, thus leading to more pain-related activity in return. The resulting effect on the patient's pain could be the difference between the ACC inhibition induced by the ACC DBS electrode, and its activation generated by a signal back from the PCC. The underlying mechanisms of DBS for pain remain difficult to assess but these results point to the fact that it is the specific connectivity of the DBS electrode which is effective in eliciting pain relief. As such, these data could potentially help to guide electrode location for the future patients based on their own brain connectivity.

Interestingly, we also found a difference with connectivity to the precuneus region. In this region too, the connectivity from the electrode was greater in patients that were not relieved by the stimulation of the ACC. This brain area is a key part of the default mode network and has been implicated in self-reference and memory, and has also been shown to be more active when viewing pictures of body parts in painful situations (Lamm, Decety et al. 2011).

Moreover, in the prefrontal cortex regions, the connectivity patterns shifted anteriorly in patients where DBS was less effective.

Conclusion: this research has helped to better elucidate the mechanisms of chronic pain relief, which is a complex phenomenon which objective and subjective components.

#149

Deep Brain Stimulation for Refractory Chronic Cluster Headache

Harith Akram (1), Sarah Miller (2), Susie Lagrata (3), Jonathan Hyam (4), Marwan Hariz (1), Manjit Matharu (5), Ludvic Zrinzo (1)

1. Unit of Functional Neurosurgery, Institute of Neurology, UCL, Queen Square, London, United Kingdom

2. Neurology, The National Hospital for Neurology and Neurosurgery, London, United Kingdom

3. Department of Neurology, The National Hospital for Neurology and Neurosurgery, London, United Kingdom

4. Unit of Functional Neurosurgery, Institute of Neurology, UCL, Queen Square, London, United Kingdom

5. Department of Neurology, Institute of Neurology, UCL, The National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom

Submitter: Mr Akram Harith (GB)

Introduction: Cluster headache (CH) is a primary, often excruciating, unilateral headache with recurrent episodes of severe pain centred on the eye with ipsilateral trigeminal autonomic features. When CH attacks occur for more than 1 year without remission or with remissions lasting less than 1 month it is defined as chronic cluster headache (cCH). 10-20% of patients are refractory to medical management. We present a prospective cohort of patients with cCH treated with posterior hypothalamic (PH) deep brain stimulation (DBS), focusing on the change in the headache load and quality of life (QoL).

Methods: Patients with refractory cCH who fulfil the ICHD-II diagnostic criteria and who had exhausted all medical treatment (and occipital nerve stimulation for some) referred to DBS multidisciplinary headache clinic at our centre underwent ipsilateral PH DBS. Clinical data was collected pre and post-treatment on regular basis. The primary outcome measure was change in the headache load (HAL). The HAL is defined as severity of headache on the visual analogue scale x duration x frequency over a 2 week period; a treatment response was identified as a 30% or more reduction in HAL. Secondary outcome measures were QoL data collected using questionnaires including the Short Form 36 (SF36) score measuring both the physical and mental component summary, the Hospital Anxiety and Depression score (HAD-A) and (HAD-D), the Migraine Disability Assessment Score (MIDAS), the Headache Impact-6 (HIT-6) score, the Beck Depression Inventory II (BDI-II) score and the EuroQol EQ-5D score.

Results: 19 patients (15 male) with a median age of 48 years (33-67 years) underwent surgery. Median follow up time was 12 months (9-48 months). 17 patients had at least one year follow up. Five patients (26%) did not respond to DBS. Within three months of surgery, the median improvement in HAL was 62% ($p=0.001$) and at twelve months was 69% ($p=0.03$). Median improvement in MIDAS at 6 months was 11% ($p=0.05$) and at 12 months 46% ($p=0.05$). HIT-6 improved by 8% ($p=0.01$) at 6 months and by 6% ($p=0.01$) at 12 months. HAD-A showed an improvement of 11% ($p=0.03$) at 6 months, and BDI-II showed an improvement of 11% ($p=0.03$) at 6 months. The physical component summary (PCS) of the SF-36 scores showed an improvement of 12% ($p=0.03$) at 6 months. EuroQol showed an improvement of 12% ($p=0.02$) at 12 months. There were no serious adverse events. One patient reported persistent diplopia, which was due to decompensation of a long-standing third nerve palsy.

Conclusion: Posterior Hypothalamic DBS appears a safe and effective treatment for cCH and should be considered for suitable patients who fail conventional treatment.

#179

Construction and refinement of a collagenase induced haemorrhagic stroke model

Philippe De Vloo (1), Kris van Kuyck (1), Johannes van Loon (2), Bart Nuttin (1)

1. *Laboratory for Experimental Functional Neurosurgery, KU Leuven, Leuven, Belgium*2. *Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium***Submitter:** Mr De Vloo Philippe (BE)

Introduction: Central post-stroke pain (CPSP) is a neuropathic pain syndrome that can occur after ischemic or haemorrhagic stroke, most typically located in the sensory thalamus. It is characterized by pain and sensory abnormalities in the body parts corresponding to the affected brain region. The current treatment mainly consists of medication. For refractory cases motor cortex stimulation and deep brain stimulation procedures have been proposed.

The lack of a valid animal model has hampered further research into CPSP, until recently a possible haemorrhagic stroke model was established. We aimed at reproducing and refining this model.

Methods: In 7 consecutive groups of 10 male Sprague-Dawley rats, we stereotactically injected 0,125 microliter of saline (control, n=7x4) or solutions containing 7 different concentrations of collagenase type IV (experimental, n=7x6) into the thalamic ventral posterolateral nucleus. Collagenase concentrations ranged from 1.14 to 4.28mg/ml.

Since collagenase degrades the endothelial collagen structure we aimed at creating a thalamic bleeding, mimicking a haemorrhagic stroke. Thermal (hot plate, cold plate) and mechanical (electronic von Frey filaments) sensitivity and motor function (rotarod) were tested at d-7,3,7,14,21,28 from surgery. Then rats were euthanised and their brains were removed, fixated, paraffin-embedded and cut into 50 micrometre thick coronal slices, which were digitally photographed. Using in-house developed software, virtual 3D brains in the Paxinos reference system were re-calculated from these images, allowing localisation and measurement of brain cavities resulting from the bleeding.

Results: In one group (concentration 1.14mg collagenase/ml) experimental rats showed thermal hypersensitivity for both warmth (sudden and gradual hot plate test) and cold (cold plate) at various time points after surgery as compared to control rats. No differences were observed for mechanical sensitivity or motor performance. In the other six groups, with higher collagenase concentrations used, no statistically significant differences were observed. In the one group showing thermal hypersensitivity the affected brain tissue was mostly restricted to the ventrolateral thalamus.

Conclusion: Using stereotactic injections of a collagenase solution we were able to create local bleedings in the ventrolateral thalamus, resulting in thermal hypersensitivity but no mechanical hypersensitivity in one experimental group, which could serve as a possible rat model for CPSP.

#253

Topography of pain and somatic sensations in the insula: a study of responses to direct electrical stimulation on children population

Vincent d'Hardemare (1), Sarah Ferrand-Sorbet (2), Georg Dorfmueller (2), Delphine Taussig (2), Jean-Baptiste thiebaut (3)

1. Neurosurgery, Fondation Ophthalmologique A. de Rothschild, Paris, France

2. Neurosurgery, Fondation Ophthalmologique A. de Rothschild, Paris, France

3. Neurosurgery, Fondation ophthalmologique A. de Rothschild, paris, France

Submitter: Mr d'Hardemare Vincent (FR)

Introduction: Few articles mention that the stimulation of the insular cortex could cause pain, and each time only adult population was studied. We here present the results of a prospective study we lead among a population of children. We compare our results to the data of the literature to try a better understanding of these anatomical connectivities between the different modalities of pain and the brain areas.

Methods: From 2009 to 2014, 58 insular cortex explorations in s-EEG were performed on children as a preoperative intractable epilepsy exploration. The implantation of depth electrodes was realised stereotactically with the robot Rosa (Medtech °). A image fusion is then done between the MRI planning and postoperative scanner. Children were explored for several days and those presenting no seizures received stimulations. We studied painful somaesthetic sensations elicited by direct electrical stimulations of the insular cortex.

Results: 11 explorations with stimulation triggered a pain. Stimulated targets are located in the upper part of the caudal insula and seem to respect topography from back to front and top to bottom: the face (3 cases), upper limb (5 cases) and lower limb (3 case). The pain may be very localised and concomitant to stimulation. 1 child described a sensation of bone pain with hallucinations. Topography results match the description done when studying an adult population. Yet, the way to achieve the s-EEG may affect the results, considering the stimuli excite axons whose orientations are difficult to determine. All stimulations are located at the portion corresponding to the granular posterior insula. Recent anatomical studies can characterise this area as the first target projection of spinothalamic pathway.

Conclusion: The posterior insula is the first cortical area involved in acute pain. Brain imaging should clarify the role of the posterior insula in pain detailing cortical areas and their connections.

#254

Electromagnetic navigation system in the percutaneous cannulation of the foramen ovale. Technical note

Vincent d'Hardemare (1), Jean Bruxelles (2), Anne Margot-Duclos (3), Maximilien Bachelart (4), Jean-Baptiste Thiebaut (5)

1. Neurosurgery, Fondation Ophtalmologique A. de Rothschild, Paris, France

2. Pain Treatment Department, Fondation ophtalmologique A. de Rothschild, paris, France

3. Pain treatment Department, fondation ophtalmologique A. de Rothschild, Paris, France

4. Neurosurgery, Fondation Ophtalmologique A. de Rothschild, Paris, France

5. Neurosurgery, Fondation ophtalmologique A. de Rothschild, paris, France

Introduction: Percutaneous cannulation of the foramen ovale (FO) allows a quite efficient and safe treatment for trigeminal neuralgia. However, technical failure to cannulate the FO despite fluoroscopy may be a significant problem. Hereafter, we evaluate the advantages of the electromagnetic navigation system for this indication.

Methods: 31 procedures were lead over the last year to realise radiofrequency thermocoagulation or balloon compression of the Gasser ganglion for idiopathic trigeminal neuralgia. Each time, a frameless stereotaxy using an electromagnetic navigation system was used to guide the percutaneous needle with a magnetic probe. Preoperatively, a head Computed Tomography (CT) scan was performed and the acquired images were imported into the navigation system.

Results: Between April 2013 and June 2014, 29 patients were treated for a trigeminal neuralgia by a percutaneous approach. For each patient, the operation was completed successfully. A total pain relief was reported immediately postoperatively. But after 10 months, 2 patients showed recurrence, also responding correctly to a second procedure. No complications were recorded. The rapidity and the safety of the cannulation of the FO have to be related: used fluoroscopy only at the end of the puncture to confirm the correct position. The total X-Ray radiation rate is then divided by 10 (average rbd 0,185 mG and 0.00322 mGym²).

Conclusion: The presented data suggest that frameless stereotaxy is a predictable and reproducible procedure, which may enhance patient security and cannulation success independent of the surgeon's experience. We now systematically use the electromagnetic guidance to locate the FO. The lower X-Ray radiations are a good sign to confirm the easiness of the procedure. We evaluate the same system navigation with a fusion between MRI and CT-scan to check the location of the probe is in the gasser ganglion. Then, we can be more accurate for the thermocoagulation.

1.1.5 Spasticity

#70

Behavioral and EEG responses to deep cerebellar stereotactic stimulation

Miroslav Galanda (1), Peter Jombik (2), Tomas Galanda (3), Jana Mistinova (4), Peter Bob (5)

1. Department of Neurosurgery, Roosevelt University Hospital, Banská Bystrica, Slovakia

2. Department of Neurology, Zvolen Hospital, Zvolen, Slovakia

3. Department of Neurosurgery, Roosevelt University Hospital, Banská Bystrica, Slovakia

4. Radiologická klinika, LFUK Radiologická klinika, Bratislava, Slovakia

5. Department of Psychiatry and UHSL, Charles University, Prague, Czech Republic

Submitter: Mr Galanda Miroslav (SK)

Introduction: The aim of this study was to assess the relation of behavioral responses with EEG activity to stereotactic stimulation of anterior lobe of cerebellum, which was applied in 48 patients for symptomatic treatment of spasticity and dyskinesias in cerebral palsy.

Methods: In every patient during test stimulation was possible to evoke clinically evident behavioral responses which depended on the parameters of stimulating current (250 Hz, 0.5- 4mA) – feeling of pleasure, relaxation and at higher current level fear accompanied with increased pathological posture of patient (overstimulation). In 5 patients were evaluated the EEG activity before and during test stimulation which evoked feeling of pleasure and fear.

Results: All five patients showed consistent and significant changes (Kruskal-Wallis $p < 0.00$) in the delta and alpha frequency bands. There was increase in the relative values of the powers of the alpha frequency and decrease in delta band during condition which evoked feeling of pleasure. Overstimulation was accompanied with opposite effect.

Conclusion: The role of the cerebellum in sensorimotor regulation is well known. But cerebellum has widespread reciprocal connections with the areas of the brain even those involved in processes of emotion and cognitive functions. Dominant alpha rhythm is important electrophysiological sign of the healthy brain function. On the other hand increase of slow activity heralds disturbed brain function. Global EEG changes observed during stereotactic cerebellar stimulation can reflect improved function of the neuronal network, which seems to be under strong influence of the cerebellum.

#122

Tibial neurotomy for lower limb spasticity in cerebral palsy

Nobuhiko Takeda (1), Takaomi Taira (1)

1. *Neurosurgery, Tokyo womens medical university, Tokyo, Japan*

Submitter: Mr Takeda Nobuhiko (JP)

Introduction: Botulinum toxin therapy (BTX) and intrathecal baclofen (ITB) have emerged and options to treat spasticity have increased. Besides such treatments, we have been performing selective peripheral neurotomy (SPN) for more than 100 patients with spasticity. This time we review efficacy and indication of SPN based on our experience in typical cases of cerebral palsy.

Methods/results: Case 1: 34-year-old woman. She was born at 37 weeks gestation. Equinovarus foot was seen since childhood and became worse gradually. Medication and botulinum toxin injections were not effective. At 34 years old, she had undergone SPN for left equinovarus foot. It was so effective that she underwent SPN for right side in the following year.

Case 2: 15-year-old boy. He was born with weight of 1950 gram and diagnosed as cerebral palsy since childhood. Bilateral equinovarus feet were seen but without treatment. As he got older, he underwent bilateral SPN.

Case 3: 30-year-old woman. She was diagnosed as cerebral palsy since childhood and had undergone orthopedic surgery. Recently spasticity of her left foot became worse and she underwent SPN.

Case 4: 15-year-old girl. She had presented with bilateral equinovarus foot from her childhood and she was diagnosed as cerebral palsy. She had visited our hospital at 5 years old. However symptom was so mild that she was just followed up. Symptom became worse as she got older and she underwent bilateral SPN.

In every patient, ankle clonus disappeared and spasticity improved. Because knee flexion remained, two patient showed crouching gait which improved naturally. Numbness of right lower limb was seen after operation and start of rehabilitation was delayed.

Conclusion: We experienced four cases of SPN and resulted in good outcome. BTX and ITB have advantage of reversibility and adjustability. On the other hand, they need frequent injections or refill of drug, which are burden for young patients. Although SPN has risk of pain and sensory disturbance and extensive rehabilitation is necessary, it is effective for young patients older than 12 years old who has willingness and enough muscle power for rehabilitation.

#153

Efficacy, safety and complication profile of the Prometra programmable pump in providing intrathecal baclofen therapy for intractable spasticity

Aristotelis V. Kalyvas (1), Marios Themistocleous (1), Nikolaos Boutos (1), Konstantinos Themistoklis (1), Stefanos Korfias (1), Damianos E. Sakas (1)

1. Neurosurgery department, Evangelismos Hospital, University of Athens, Athens, Greece

Submitter: Mr Kalyvas Aristotelis V. (GR)

Introduction: The impact of intrathecal Baclofen (ITB) therapy, via an implanted pump, for both spinal and cerebral spasticity has been well documented in various studies over the years. Although there are trials assessing the accuracy and efficacy of the Prometra programmable pump system for intrathecal administration of morphine sulfate to treat chronic pain, none has done so for ITB administration in treating spasticity. Consequently, we set out to determine the efficacy, safety and complication profile of the aforementioned programmable pump (Flowonix).

Methods: This is a retrospective observational study using data collected from case notes and existing departmental databases of Evangelismos Hospital, Athens, Greece. Specifically, patients with intractable spasticity who responded positively to a trial dose of baclofen and treated with ITB therapy via the Prometra programmable pump (20ml) (n=40), between December 2011 and May 2014, were included in the study. A predefined data extraction form was applied to extract pertinent study information (gender, age, underlying pathology, follow-up period, daily concentration) and outcome measures (pre- and post-operative modified Ashworth scale values, technical considerations/difficulties during the operation or refilling procedure, revisions, complications).

Results: 40 patients (24M/16F) with a mean age of 43.3y (range=18-79) underwent implantation of the programmable pump. Spastic paraparesis was encountered in 22 patients, spastic quadriparesis in 11 and spastic hemiparesis in 7 of them. Underlying aetiologies of the spasticity were cerebral palsy (n=12, 30%), multiple sclerosis (n=10, 25%), cerebral vascular accident (n=5, 12.5%), hereditary spastic paraparesis (n=3, 7.5%), CNS infection (n=3, 7.5%), traumatic spinal injury (n=2, 5%), neglected cervical or thoracic spondylosis (n=2, 5%), traumatic brain injury (n=1, 2.5%), posterior fossa mass lesion (n=1, 2.5%) and idiopathic spasticity (n=1, 2.5%). The mean follow-up period was 16.7 months. All 40 patients experienced improvement in their spasticity as evidenced by reduction in the modified Ashworth scales (MAS) scores. The mean daily concentration of intrathecal baclofen administration was 90µgr (40-220 range). Operative technical difficulties considering the introduction, advancement and anchoring of the catheter were not an issue in any of the included participants. The refilling procedure and programming were uncomplicated in all patients and no case of over-infusion has been reported. 4 patients underwent 6 catheter revisions due to catheter fracture and one patient underwent explantation of the device due to implant site infection. Seroma of the wound site (absorbed over 3 weeks period) was documented in one patient.

Conclusion: The Prometra programmable pump was shown to provide effective ITB therapy in all included patients. The reported complication profile, particularly the device-related complications were consistent with complications documented in our department's database and in other studies involving various programmable pumps for ITB therapy. Finally, its intra-operative ease of handling combined with its convenient manipulation during the refilling procedure and programming render its use simple.

#154

Infectious complications and treatment options in intrathecal baclofen delivery systems

Konstantinos Themistoklis (1), Nikolaos Boutos (1), Marios Themistocleous (1), Aristotelis V. Kalyvas (1), Damianos E. Sakas (1)

1. Neurosurgery department, Evangelismos Hospital, University of Athens, Athens, Greece

Submitter: Mr Kalyvas Aristotelis V. (GR)

Objectives: The scope of this study was to investigate the rate of infections among patients who underwent surgical placement of intrathecal baclofen pump and the possible treatment options.

Methods: A retrospective analysis was performed in patients who underwent surgical placement of intrathecal baclofen pump in Evangelismos Hospital from 2001 to 2013. We registered the rate of infections and factors such as age, gender, diagnosis, grade of spasticity according to the modified Ashworth scale and other complications related with the baclofen pump placement. We differentiated between superficial skin infections, deep infections affecting the subcutaneous tissues, CNS infections and identified the causative agent. We also registered the period, either post-operative or during follow up care, in which the infection appeared. Furthermore, we evaluated the different treatment options.

Results: A series of 275 patients suffering from spasticity, which was caused from different underlying pathologies, were treated with the implantation of a baclofen delivery system. Among them, 6 patients were presented with superficial, 1 with deep and 4 with CNS infections. The patients presented the infection during the post-operative period were 10 and during the follow up period 1. The causative agent was *Staphylococcus*, *epidermidis* or *capitis* and in one case *Pseudomonas aeruginosa*. In all cases antibiotics were administrated either by intravenous or intrathecal way and in 5 cases surgical intervention was performed.

Conclusion: The treatment of spasticity with implantable baclofen pumps remains a safe method, even if severe infections occur. Usually, the administration of intravenous antibiotics, without the explantation of the pump, is adequate for the treatment of the infection.

1.1.6 Neuroimaging

#87

In vivo ultra-high field tractography and subdivision of the human subthalamic nucleus to improve deep brain stimulation

Birgit Plantinga (1), Alard Roebroek (2), Dimo Ivanov (2), Kâmil Uludağ (2), Mark Kuijf (3), Bart ter Haar Romeny (4), Yasin Temel (5)

1. Department of neuroscience, Maastricht University, Maastricht, Netherlands

2. Department of cognitive neuroscience, Maastricht University, Maastricht, Netherlands

3. Department of neurology, Maastricht University Medical Center, Maastricht, Netherlands

4. Department of biomedical image analysis, Eindhoven University of Technology, Eindhoven, Netherlands

5. Department of neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

Submitter: Melle Plantinga Birgit (NL)

Introduction: The subthalamic nucleus (STN) is an important target for deep brain stimulation (DBS) surgery in Parkinson's disease. Although DBS alleviates motor symptoms, it is also associated with side-effects, which are expected to be related to a suboptimal position of the electrode within the STN. With current clinical MR imaging techniques, the small STN and especially its functional subdivisions, cannot be identified accurately enough to solely rely upon for targeting.

However, with the introduction of ultra-high field (7T or higher) MRI scanners, higher resolution, and higher contrast imaging becomes available. Furthermore, it offers the option to investigate functional subdivisions of the STN in high detail based on its structural connectivity. This is important to improve targeting of only the motor region of the STN. In this study we investigate this high-resolution structural connectivity of the STN and its functional subdivision, based on 7T MRI data.

Methods: This study was approved by the local ethics committee of the Maastricht University Medical Center. Four healthy subjects (age 57-70 years), were scanned on a 7T MRI scanner (Magnetom 7T, Siemens, Germany). The scan protocol consisted of 0.5 mm isotropic gradient echo (GE), and 1.5 mm isotropic diffusion weighted images with 60 directions with a b-value of 2000 s/mm² and 6 additional b₀ volumes. Another 6 volumes were recorded with reversed phase-encode blips to correct for susceptibility distortions with FSL's topup in conjunction with eddy current and motion correction with FSL's eddy tool. The STNs were manually delineated from the GE images using ITK-SNAP. They were then coregistered along with the GE image to the corrected diffusion weighted images using FSL's linear image registration tool. Fiber tracking was performed from the STNs, using diffusion tensor based deterministic fiber tracking implemented in the MRtrix package. Fibers with distinctly different destinations were manually selected to investigate their origin within the STN.

Results: Among the fibers emerging from the STNs, connections to the anteromedial side of the internal globus pallidus (GPi), the premotor cortical areas, and the frontotemporal cortical areas, were found in all 8 STNs. The fibers running to the GPi emerged from the anteromedial side of the STN for all 8 STNs. The majority of the fibers running to the premotor areas originated from the posterolateral side of the STN in 7 STNs and from the posteromedial side in 1 STN. The majority of the fibers running to the frontotemporal areas emerged from the dorsolateral side of the STN in 7 STNs and from the ventrolateral side in 1 STN, with no distinct anterior or posterior origin.

Conclusion: These results show a subdivision of the STN based on its structural connectivity. The connections of the anteromedial STN with the limbic anteromedial GPi and those of the posterolateral STN with the premotor cortical areas, suggest that the STN can be divided in a limbic anteromedial and a motor posterolateral part. These results also suggest that ultra-high field diffusion MRI may aid in improving the outcome of DBS surgery by accurate and subject specific targeting of the functional area of interest.

#163

Effect of direct visualization of GPi using MDEFT MR sequence on targeting and location of the active electrode.

Andreas Nowacki (1), Michael Fiechter (1), Jens Fichtner (1), Markus Oertel (1), Ines Debove (2), Lenard Lachenmayer (2), Michael Schüpbach (2), Roland Wiest (3), Claudio Pollo (1)

1. Neurosurgery, University Hospital Bern, Bern, Switzerland

2. Neurologie, University Hospital Bern, Bern, Switzerland

3. Neuroradiologie und Interventionelle Radiologie, University Hospital Bern, Bern, Switzerland

Introduction: DBS of the Globus pallidus internus (GPi) has been shown to be effective in the treatment of dystonia and Parkinson's disease. Recent advances in different MRI sequences have provided direct visualization of the GPi. Whether and how it has changed the way we target and place our electrodes within the GPi compared to standard atlas coordinates is still not clearly documented. The objective of this study is to prospectively study the impact of direct visual targeting on the final position of the active electrode using a T1-weighted Modified Driven Equilibrium Fourier Transform (MDEFT) sequences which show a good contrast of the basal ganglia with distortion.

Methods: 13 consecutive patients considered for bilateral GPi DBS for dystonia (6) or Parkinson's disease (7) were included in this study. Preoperative targeting of the GPi was performed visually on MDEFT sequences as well as using standard atlas coordinates (Schaltenbrand and Wahren) and fused with stereotactic CT scan. Postoperative CT imaging was performed to calculate the location of the implanted leads as well as the active electrode(s). (iPlan, Brainlab, Germany). The coordinates of both visual- and atlas-based targets were compared. The stereotactic coordinates of the lead and active electrode(s) were calculated and co-registered with the preoperative segmented GPi. T Test was performed to compare the populations.

Results: We found a significant difference in the anterior-posterior (AP) and lateral (LAT) coordinates between visual (AP = 1.45 ± 0.79 , LAT = 19.69 ± 1.78) and atlas-based target (AP = 2.73 ± 0.45 , LAT = 21.36 ± 1.24). Furthermore, there was a significant difference in the LAT coordinate between dystonic (LAT = 18.76 ± 1.13) and parkinsonian patients (LAT = 20.78 ± 1.85) only in the visual targeting group. In the visual targeting group the active contacts were located in the inferior and posterior part of the GPi, which corresponds to the motor part of this nucleus.

Conclusion: Compared to atlas-based targeting, direct visual targeting using MDEFT shows a significantly higher variability of the laterality of the target coordinates and a significant shift in the posterior and medial direction. Active electrodes were found in the posterior and inferior part of the structure, indicating that visual targeting provides a more precise targeting according to the patient's individual anatomy of the GPi.

1.1.7 Neuro-oncology

#72

ARTIFICIAL INDUCTION OF CORTICAL PLASTICITY BY HIGH FREQUENCY CORTICAL STIMULATION PERMITS TO INCREASE RESECTION OF BRAIN TUMORS LOCATED IN ELOQUENT AREAS

Juan A. Barcia (1), Paola Rivera (1), Osman Salazar (1), Sandra Sanchez-Casarrubios (1), Marcos Ríos-Lago (1), Mercedes González-Hidalgo (2), Miguel Yus (3), Juan Alvarez-Linera (4), Josue Avecillas-Chasin (1)

1. Neurosurgery, Hospital clinico San Carlos, Madrid, Spain

2. Neurophysiology, Hospital clinico San Carlos, Madrid, Spain

3. Neuroradiology, Hospital clinico San Carlos, Madrid, Spain

4. Neuroradiology, Hospital Ruber Internacional, Madrid, Spain

Introduction: Extent of resection is the main factor in the prognosis of WHO grade 2 and 3 gliomas. This is limited by the presence of eloquent areas near or within the tumor. However, if those functions could be artificially displaced away from the tumor, a greater extent of resection could be feasible.

Methods: We present 5 cases of gliomas localized at eloquent areas (one anaplastic astrocytoma at Broca's area, one left frontal oligodendroglioma, one left temporoparietal anaplastic oligodendroglioma at Wernicke's area, one anaplastic astrocytoma at the primary motor area, and one left frontal astrocytoma compromising Broca's and primary motor area). These patients were operated awake and the tumors could not be resected according to established cortical stimulation standards. A cortical grid of electrodes was placed over the tumor and inhibitory continuous stimulation (130 Hz, 60 us) was continuously applied to the grid's functional contacts (HFCS). The intensity was set daily to the threshold of inducing a mild functional deficit, while the patient performed an intensive rehabilitation of the function.

Results: When an intensity of 10 mA was achieved in all active contacts producing no deficit (usually after 3 weeks), the patients were reoperated. This procedure permitted an extended resection of the tumor. Functional studies showed a displacement of the functions to other locations in neighboring areas or at the contralateral hemisphere.

Conclusion: We present evidence of artificial enhancement of plasticity by HFCS in tumors containing eloquent areas, permitting an extensive resection, maintaining the functions and improving the survival and quality of life of the patients.

#219

ACCURACY OF ELECTROMAGNETIC FRAMELESS STEREOTACTIC BRAIN BIOPSY

Alessandro Dario (1), Jacopo Poli (2), Angelo Rusconi (2), Lidia Bifone (3)

1. *Functional Neurosurgery, Varese Regional Hospital, Varese, Italy*2. *Unit of Functional Neurosurgery, Ospedale di Circolo- Fondazione Macchi, Varese, Italy*3. *Ospedale di Circolo- Fondazione Macchi, Unit of Functional Neurosurgery, Varese, Italy*

Objective: To evaluate in a prospective study the precision and effectiveness of electromagnetic frameless stereotactic brain biopsy and to identify risks and their resolution

Methods: From 2009 to 2013 at our Hospital we performed 82 electromagnetic frameless stereotactic brain biopsies using the Stealth Station AxiEM Neuronavigation System (Medtronic Inc, USA).

Ten cutaneous markers were used to create the registration. Age ranged from 39 to 76 years (mean age 53 years); 48 patients were males, 34 females. The preoperative neuroradiological examination was a cerebral MRI in all patients but three. All patients after biopsy underwent cerebral CT-scan between two hours after surgery to evaluate the right trajectory. This was evaluated by images fusion with neuronavigation system using preoperative MRI with postoperative CT-scan. The surgical complications were reported.

Results: The main neoplasm side was found to be frontal in 32 patients, parietal in 18 patients, temporal in 12 patients, occipital in 10 patients, basal ganglia in 5 patients, 5 a diffuse extension.

The histology examination showed :58 Glioblastomas, 4 Anaplastic astrocytoma, 8 WHO 2° astrocytoma (2 in peripheral side of malignant glioma), 2 abscesses, 1 inconclusive for grading (reactive gliosis in malignant glioma), 5 lymphomas, 4 metastases.

The targeting was wrong in 3 cases of parietal (1) and occipital (2) side in the first 12 cases with underestimation of the astrocytoma grade. No postoperative deaths occurred; two patients (2,4%) showed symptomatic postoperative haemorrhage, whereas seven patients (8.5%) had no symptomatic bleeding. Postoperative pneumoencephalus was recorded in ten patients (12%).

Conclusion: In patients with fronto-temporal lesions the precision of this biopsy technique was obtained in all cases. In parieto-occipital lesion particular care must be used to avoid displacements of the reference device by surgical drape. This event can cause wrong lesion targeting. The complications rate seems to equivalent to other biopsy techniques.

#279

ZEB1 mediates hypoxia driven- glioma invasion and is associated to neural stem cellUD Kahlert¹, FA Siebzehrnub², EE Bar³, CG Eberhart¹ and J Maciaczyk⁴¹ Department of Pathology, Division of Neuropathology, Johns Hopkins Hospital, Baltimore, MD, USA² Department of Neurosurgery, University of Florida, Gainesville, FL, USA³ Department of Neurosurgery, School of Medicine, Case Western Reserve University, Cleveland, OH, USA⁴ Department of Functional and Stereotactic Neurosurgery, University Medical Center Düsseldorf, Germany

Introduction: Hypoxia is thought to induce migration in many neoplasms, often by promoting epithelial-to-mesenchymal transition (EMT), but the mechanisms by which it affects brain tumor invasion is less well understood. In particular, little is known about the possible role of EMT-associated factors in hypoxia-mediated induction of migratory phenotype in gliomas. In this project we investigate the possible role of EMT-changes as a molecular mechanism leading to increased motility of malignant gliomas in hypoxic environment.

Methods: Migration and invasion of GBM-derived cell lines (n5) cultivated as spheres under atmospheric oxygen (21% O₂) and acute (14h) or chronic (48h) hypoxia (1% O₂) have been assessed in Boyden Chamber-based *in vitro* assay. Digoxin has been used to inhibit the HIF-1-mediated hypoxic response. ZEB1 knockdown has been achieved using lentiviral sh-RNA delivery. The quantitative gene expression and protein analyses of EMT activators have been performed according to standard real-time qPCR or Western Blot protocols respectively. Standard immunohistochemistry on formalin-embedded GBM-patient tumor samples including antigen retrieval and Haematoxylin counterstain to detect ZEB1-positive cells has been applied. Moreover, the prognostic value of EMT-associated factors in a cohort of GBM patients has been assessed based on publically available genomic and clinical databases (TCGA and Rembrandt). Additionally we investigated the expression of ZEB1 in the human fetal-derived brain samples.

Results: Hypoxia led to a significant increase of invasion (up to 6 fold) in all tested cell lines, as assessed by Boyden Chamber-based assay. This was accompanied by an induction of EMT activators including ZEB1, SNAI1 and TWIST1 (up to 8 fold) as compared to normoxic cultures. Digoxin treatment resulted in clear abolition of this phenomenon. Moreover, ZEB1-knockdown has significantly reduced the invasive behavior of the cells. The histological analysis of patient-derived GBM samples revealed an abundance of ZEB1 positive cells in hypoxic, peri-necrotic tumor areas. Furthermore, the up-regulation of EMT activators such as TWIST1, SNAI1 and SNAI2 was found as a hallmark of the most aggressive, mesenchymal subgroup of GBMs in the analysis of TCGA and Rembrandt datasets. Interestingly, ZEB1 was also found in a subset of cells in subventricular zone and cerebellar external germinal layer, suggesting a molecular mechanism of neural precursor cell migration during the early developmental stages similar to the one observed in brain tumors.

Conclusion: Hypoxia increases the invasion capacity of GBM-derived cells inducing mesenchymal developmental program by the process of epithelial-to-mesenchyme-like transition. Inhibition of the hypoxic, HIF-1-mediated molecular changes protects from over-expression of EMT activators and might contribute to the development of the novel therapeutic strategies aiming at the elimination of the migratory cell subpopulation, and thus preventing the tumor dispersion.

1.1.8 Neurotransplantation

#109

Stereotactic planning software for human neurotransplantation: suitability in 22 surgical cases of Huntington's disease.

William Omar Contreras Lopez (1), Guido Nikkhah (2), Elisabeth Schultke (3), Luciano Furlanetti (4)

1. *Functional and Stereotactic Department, University of Sao Paulo, Sao Paulo, Brazil*

2. *Functional Neurosurgery, Freiburg University/Erlangen University Clinic, Erlangen, Germany*

3. *Functional and Stereotactic Department, Freiburg University Clinic, Freiburg, Germany*

4. *Functional and Stereotactic Neurosurgery, Freiburg University Clinic, Freiburg, Germany*

Introduction: Intrastriatal neural transplantation using multiple grafts is an experimental approach to the treatment of Huntington's disease (HD). Brain atrophy makes stereotactic plans in these patients a tedious procedure with a risk of suboptimal spatial distribution of the grafts in transplantation procedures. Here we present a self-developed software to optimize the surgical stereotactic planning for bilateral neurotransplantation procedures. It allows close to symmetrical distribution of the stereotactic coordinates in relation to the mid-commissural point (MCP), proposing automatically the planning coordinates for the first transplanted hemisphere and mirrored coordinates to be used in the contra-lateral hemisphere.

Methods: Twenty-two consecutive HD patients underwent bilateral stereotactic striatal transplantation. Two caudate nucleus and four putaminal tracks were planned bilaterally. For the second, contra-lateral transplantation, the coordinates were mirrored in order to determine contralateral targets and trajectories. Intra-individual comparison between software given coordinates and finally used coordinates was performed.

Results: No statistical significance was found comparing a) the differences between coordinates proposed by the software and the final coordinates and b) the distribution of the transplantation sites in relation to the midline for the right vs. left hemisphere. No intra- or postoperative transplantation-related adverse events occurred.

Conclusion: The use of model-based and mirrored coordinates allowed optimal spatial distribution of the grafts. Minor changes were required comparing right to left coordinates giving proof-of principle. The initial use of the software suggests that it may be useful in experimental transplantation trials where neural cell grafts are to be implanted into predefined target sites in the human brain, whether unilateral or bilateral.

1.1.9 Radiosurgery

#26

Radiosurgery for large arteriovenous malformations.

Roman Liscak (1), Tomas Chytka (1), Dusan Urgosik (1), Gabriela Simonova (1), Josef Vymazal (2)

1. Stereotactic and radiation neurosurgery, Na Homolce Hospital, Prague, CzechRepublic

2. Radiodiagnostic department, Na Homolce Hospital, Prague, CzechRepublic

Introduction:

Treatment of large AVMs is a challenge and effectiveness of radiosurgery decreases with increasing treatment volume. We have analyzed and compared single session treatment for AVMs bigger than 15 cm³ to a staged treatment, when volume of large AVM was divided into 2 or more compartments and treated subsequently within a few months intervals. In case, that complete obliteration was not achieved within a 3 years, repeated radiosurgery was considered.

Methods and results: Between 1993 and 2011, gamma knife radiosurgery was performed on 49 patients with large AVMs (from the group of 1015 AVMs). 26 of them were treated in a single session, their volume ranged 15,1-27, median 18,1 cm³, marginal dose ranged 10-17, median 15 Gy. Complete obliteration was achieved in 6 (23%) of them, in 14 patients the treatment was repeated median 38 months after the first treatment, 10 of them later achieved complete obliteration, median 77 months after initial treatment. Overall, 62% of patients finally achieved cure. Rebleeding in latent period appeared in 3 patients and symptomatic collateral edema in 2 (7,7%).

23 patients were treated in a staged way, the interval between staged treatment was usually 6 months. Their volume ranged 13,2-46,6, median 23,3 cm³, volume for one stage ranged 4,5-31,3, median 11,7 cm³, marginal dose ranged 10-18, median 17 Gy. Complete obliteration was achieved in 4 (17%) of them, in 9 patients the treatment was repeated median 53 months after the first treatment, and the third retreatment was performed in 2 patients 98, resp. 102 months after the first treatment. 5 of them later achieved complete obliteration. Overall, 9 (39%) of patients finally achieved cure 48-153, median 81 months after the first treatment. Rebleeding in latent period was not observed in any of these patients and symptomatic edema in 1 (4,3%).

Conclusion: Radiosurgery of large AVM is a valuable treatment option either as a single session treatment or staged treatment with reasonable chance for cure and low risks of complications.

#44

Long term visual outcome after radiosurgery in 97 patients affected by anterior skull base benign meningiomas

Marcello Marchetti (1), Stefania Bianchi (2), Valentina Pinzi (3), Ida Milanese (3), Luisa Fumagalli (3), Achille Bergantin (4), Angelo Franzini (1), Francesco Di Meco (1), Laura Fariselli (3)

1. Neurosurgery, Fondazione IRCCS Istituto Neurologico C. Besta, Milano, Italy

2. Neuroophthalmology Unit, IRCCS Istituto Auxologico Italiano, Milano, Italy, Milano, Italy

3. Radiotherapy Unit, Dept. of Neurosurgery, Fondazione IRCCS Istituto Neurologico C. Besta, Milano, Italy

4. CyberKnife Centre, Centro Diagnostico Italiano (CDI), Milano, Italy

Introduction: The concern about radiation induced optic neuropathy (RION) strongly characterized the recent past. This has probably been the main limit to a wider diffusion of radiotherapy ND radiosurgery as treatment of meningiomas involving the anterior optic pathways.

In spite of this consideration, during the last few years the radiotherapy activity for such lesions is continuously increasing.

The aim of the present study is to define the risk of RION on a medium to long term follow-up period in a large series of patients treated by radiosurgery.

The efficacy of the treatment is also investigated.

Methods: The visual outcome of 97 patients which underwent radiosurgery due to a meningioma involving the anterior optic pathways has been retrospectively evaluated.

Patients with a minimum follow-up period longer than 12 months were included.

Sixteen patients had a single session radiosurgery (sSRS) with a mean dose of 12 Gy (range 8-13 Gy; median 13 Gy). In these cases the mean tumour volume was 4,9 cc (range 0,3-10,5 cc; median 3.6 cc). Eighty-one patients underwent a multi-session radiosurgery (mSRS). The mean prescription dose was 24 Gy (range 15-30Gy; median 25Gy), the mean tumour volume was 9,5 cc (range 0,5-65 cc; median 6,5 cc). The visual outcome was evaluated in all cases. All the included patients had at least a pre-treatment and a last follow-up visual function assessment.

Furthermore local control has been analyzed.

Results: The mean follow-up is 43 months (range 12-96 months; 56 patients f-up \geq 36 monts; 23 patients f-up \geq 60 months). Compared to the baseline the visual function improved in 24 patients (24 %) and was unchanged in 65 (68 %). Seven patients worsened 8 (8 %). Three out of these experienced a tumour progression. Only two patients with no progression disease developed a "de novo" visual deficit. At the analysis time, the overall local control was 94 %. Eighteen lesions (18%) showed a partial shrinkage, seventy-three (72%) were stable and 6 patients (6%) experienced a progression of the disease.

When observed, the tumour progression always occurred later than 36 months post-treatment.

Conclusion: The study confirms the low risk of radiation induced optic neuropathy both in case of sSRS and mSRS. Multisession radiosurgery makes also the larger lesions manageable.

The high local control rate and the low toxicity suggest that radiosurgery could be proposed also as a primary treatment.

#120

X-knife stereotactic radiosurgery for cerebral AVM: a single centre experience in Hong Kong

Benedict Beng Teck Taw (1), Ho Fun Victor Lee (2), Kwan Ngai Hung (1)

1. Neurosurgery, Queen Mary Hospital, Hong Kong, Hong Kong SAR China

2. Clinical Oncology, Queen Mary Hospital, Hong Kong, Hong Kong SAR China

Introduction: This is a retrospective review of the effectiveness, safety, complications of LINAC based X-knife stereotactic radiosurgery for the treatment of cerebral AVM in Queen Mary Hospital, Hong Kong.

Methods: Retrospective search through medical records of a single institution.

From 2003-2013, all patients who received X-knife stereotactic radiosurgery for cerebral AVM were included.

Demographics, presenting symptoms, size of AVM, Spetzler-Martin grading, dosages, complications, follow-up imaging were reviewed.

Results: 33 Patients received X-knife stereotactic radiosurgery for cerebral AVM in a 10 yr period between 2003-2013. There were 13 patients had AVM that had diameters less than 3cm, 17 patients between 3-6 cm, and 3 patients with diameter more than 6 cm. There were 12 patients with Spetzler-Martin grading 5-6, 9 patients between 3-4 and 8 patients less than 3. 19/33 of the patients received 18Gy@80%IL, with 12 patients received 13-17Gy and 4 patients received more 19-22.5Gy. Follow-up ranged from 1 year to 10 years with a median follow-up of 5 years. All patient underwent MRI or DSA follow up imaging. At 3 year MRI/DSA follow-up, we recorded a 18/33 (55%) of obliteration or reduction in size of AVM, and 12/33 (36%) total obliteration rate. 13 patients' AVM remained unchanged and 2 patients had increased in size. 21/33 (64%) of the patients reported no ill effects from the radiosurgery. 7 patients suffered from symptomatic cerebral oedema requiring a course of medical treatment for reversal of symptoms. 2 patients suffered from seizures as a result from the X-knife. There were 3 patients (9%) that had intracerebral haemorrhage from the AVM after receiving X-knife. 2 of the 3 patients requiring surgery and one patient who bled died as a result.

Conclusion: From our experience, X-knife radiosurgery for cerebral AVM offer a reasonable success rate in reduction in size or obliteration of the the AVM with the majority of the patient suffering no ill side effects. It is a feasible option of treatment particularly if the risk for open surgery is deemed to be too high. It does however carries some risks of cerebral oedema and intracranial haemorrhage. Our results of total obliteration rate of only 36% seem quite low in comparison to other reports of 80-90%. This maybe the fact that some of our AVM's were quite large in size and high in Spetzler-Martin grading. Other factor maybe the relatively short follow up. Our haemorrhage rate of 9% again also seem quite high, compare with the 2-5 % from literature. This may be due to our small sample size. A more prolonged follow-up and more patients in future studies may perhaps be able to rectify the above.

#147

Gammaknife radiosurgery in pituitary adenomas: A 10-year single centre study of 150 cases.

Anne Balossier (1), Gustavo Touzet (2), Nicolas Reyns (2), Thierry Sarrazin (3), Christine Cortet-Rudelli (4), Serge Blond (2)

1. Service de Neurochirurgie, CHU de Caen, Caen, France

2. Service de Neurochirurgie, Centre Gamma-Knife, CHRU de Lille, Lille, France

3. Service de Radiothérapie, Centre Oscar Lambret, CHRU de Lille, Lille, France

4. Service d'Endocrinologie, Clinique Marc Linquette, CHRU de Lille, Lille, France

Introduction: Stereotactic radiosurgery has emerged in the last decade as a practical therapeutic option for pituitary adenomas after transsphenoidal surgery and/or medical treatments. Its low complication, high tumoral and hormonal control rates have established this technique as the main second line treatment option, nowadays replacing radiotherapy.

Methods: We report a retrospective series of 150 patients treated by Gammaknife radiosurgery for residual pituitary adenomas at the CHRU de Lille, France from 2004 to 2013.

Results: Mean age was 46 years old (range: 15-82; median: 46) and sex ratio 1.2 F/M. 51 patients were excluded from this study due to a lack of follow-up. Out of the 99 patients followed, there were 32 GH adenomas, 28 ACTH adenomas, 10 prolactinomas, 6 FSH-LH adenomas and 23 nonsecreting adenomas. The average marginal radiation dose was 24Gy (range: 15-28Gy). The mean follow-up was 40 months. Remission was observed in 40.0%, hormonal control in 78.6% and tumoral control in 100% of the cases. Prognostic factors of remission were the type of adenoma (ACTH > GH > prolactinoma) and the marginal radiation dose for GH adenomas (> 30Gy). The average remission delay was 22 months depending on the type of adenoma (ACTH < GH < prolactinoma). Complications included visual field alteration (2.0%), decreased visual acuity (3.0%), and induced hypopituitarism (15.2%). No other complications were observed. No prognostic factors were found regarding the risk of complications.

Conclusion: The results of this study are consistent with the results of the literature. In this series, radiosurgery has allowed hormonal and tumoral control associated with a low rate of complication compared to conformational radiotherapy. This technique is indicated for residual adenomas or in case of contraindications to surgery or medical treatments. Its role as a first treatment option has still to be proved.

#162

Is there a role for gammaknife stereotactic radiosurgery In Grade 4 acoustic schwannoma?

Highlight from a case series of 86 patients

Michel Lefranc (1), Romain Carron (2), Pierre Yves Borius (2), Xavier Murraciale (2), Jean Marc Thomassin (3), Pierre Hugues Roche (4), Jean Regis (2)

1. Neurosurgery, CHU Amiens, Amiens, France

2. Departement of stereotactic radiosurgery – Gamma-unit, CHU la Timone, Marseille, Marseille, France

3. ORL, CHu La Timone, Marseille, France

4. Neurosurgery, Hopital Nord, Marseille, France

Introduction: It is commonly admitted that Stade 4 acoustic schwannoma (Koos classification) are indication for microsurgery removal or combined radio-microsurgery. However, the place of gammaknife stereotactic surgery (GK-SRS) in primary intention - or when the re-evolution of the residual compresses the brainstem - has not been well evaluated. Our purpose is to report our large case series of patients with grade 4 acoustics schwannoma treated by GK-SRS.

Methods: We report all patients treated in Our department between 1996 and 2011 from Stade 4 acoustic schwannoma treated by GK-SRS with a minimal follow-up of 3 years.

Results: 94 patients with grade 4 schwannoma were treated. 4 patients were lost in follow-up, 2 benefited from only 2 years of follow-up and 2 died within 2 years but without any link with the tumour. 86 patients benefited from GK-SRS with a minimal follow-up of 3 years. Mean follow-up was 6,2 years. Patients mean age at the time of GK-SRS was 54,6 years old (range 23-84) and sex ratio was 0,6. Before GK-SRS, there was no patient with brainstem dysfunction. 16 patients benefited of ventricular derivation before GK-SRS and 14 had 1 or 2 previous microsurgery of the tumour. At the time of the GK-SRS there was no patient with raised intracranial pression. 38 patients had an effective hearing before treatment (classe 1 or 2 Gardner Robertson classification). Only one patient presented mild fifth nerve nevralgic pain before GK-SRS.

78 patients (90,7%) presented controled tumour without any clinical deterioration. For All these patients we do not report any toxicity – brainstem nor cranial nerve - linked to irradiation. 25 (65,8%) patients retained an effective hearing.

8 (9,3%) patients presented tumour growth and needed microsurgery removal in 7 cases and ventricular derivation in 1 case.

Conclusion: In regard of our large series, GK-SRS appears to be a safe and effective therapeutic option for stade 4 acoustic schwannoma for patients who do not present any brainstem nor cranial nerve dysfunction.

#201

LINAC radiosurgery for vestibular schwannomas: fusion optimization with FIESTA MRI and high definition CT improves hearing preservation rate

Ouzi Nissim (1), Roberto Spiegelmann (1), Leor Zach (2), Yaakov Lawrence (3), Raphael Pfeffer (4)

1. Neurosurgery, Chaim Sheba Medical Center, Ramat Gan, Israel

2. Radiation Oncology, Chaim Sheba Medical Center, Ramat Gan, Israel

3. Radiation Oncology, Chaim Sheba Medical Center, ramat gan, Israel

4. Radiation Oncology, Assuta Medical Centers, Tel Aviv, Israel

Introduction: In LINAC radiosurgery, stereotactic computerized tomography (CT) is key to both spatial localization of the target and dosimetric calculations, while target definition relies primarily on MRI imaging. Consequently, the precision of MRI to CT fusion is crucial to accurate radiation delivery. Older radiosurgery treatment-planning software packages resorted to scaled-down image resolution to enable fast image manipulation. In those images, visual assessment of fusion was limited since zooming-in resulted in pixelation. Newer software such as Iplan (Brainlab, Munich, Germany) have largely resolved this shortcoming. Higher resolution MRI and CT images have empowered the user to see finer detail in fused data sets. Since they became available, we frequently detect spatial mismatches in automatic fusion of MRI to CT. These inaccuracies are seen particularly in posterior fossa structures and the close-to-surface areas of the brain. In the posterior fossa they are probably related to the paucity of mutual information between the imaging modules (conventional CT and T1-weighted MR). Inaccurate fusion generates faulty localization of the target outlines (obtained from MRI) on the CT, and reduced irradiation conformality.

Functional hearing loss is the most frequent complication of stereotactic radiosurgery for vestibular schwannomas. Fusion inexactitudes could contribute to this complication by resulting in excessive radiation exposure of the acoustic nerve. We have postulated that better tumor localization should translate into improved hearing preservation rates following radiosurgery.

Methods: As standard procedure, FIESTA (CISS) and T1 with Gadolinium were used by us for tumor delineation in LINAC stereotactic radiosurgery since the early 2000s. As of January 2011, high definition (HD) CT (0.3mm Slice thickness) has been used for tumor localization, instead of 1mm slice thickness CT used earlier. Fusion quality was best assessed and manually optimized around the target area by comparison of high resolution CT of the posterior fossa to FIESTA (CISS) MRI, since both data sets could exquisitely define the anatomical structures around the IAC, such as the cochlea and the labyrinth. No other parameter in our radiosurgical routine was changed (patient selection, dose, irradiation paradigm, follow up).

Results: Of the 133 patients with VS so treated from January 2011 until April 2013, 86 (65%) had functional hearing. Of those, 59 had hearing status follow up after SRS. Their hearing outcome following SRS was compared with that of a second group of patients treated from January 2009 through December 2010, previous to the addition of MRI FIESTA/CISS TO HD CT fusion. In this second group, of the 89 patients treated, 48 had pre-treatment functional hearing and 41 of them were available for hearing follow up.

46 of the 59 patients (78%) in the first group had functional hearing preservation while only 20 of the 41 patients (49%) in the second group retained functional hearing. This difference was statistically significant (< 0.002 Fisher exact test).

This improved rate of hearing preservation did not compromise actuarial tumor control rate which was 95% in both groups.

Conclusion: A source of hearing loss after LINAC radiosurgery for VS seems to have emanated in the past from fusion related imprecisions leading to excessive exposure of the cochlear nerve to irradiation. Using high definition CT matched to CISS/FIESTA MRI images can mitigate this undesired effect by enabling fine manual optimization of fusion around the target area. Better fusion improved hearing outcome after LINAC radiosurgery in our series.

#221

STEREOTACTIC RADIOSURGERY FOR BRAIN AVMs: OUTCOME ANALYSIS

Antonio Gonçalves Ferreira (1), Ana Raquel Escolástico (1), Herculano Carvalho (1), Rosário Vicente (1)
1. Radiotherapy, Centro Oncológico Dr^a Natália Chaves, Lisboa, Portugal

Introduction: Stereotactic Radiosurgery (SRS) has an important role in the treatment of AVMs. The aim of this study was to review the outcome of patients treated to brain AVMs in our center by SRS, taking into account: 1) the percentage of complete obliteration after 2, 3, 4 and ≥ 5 years in relation to the radiation dose, AVM localization and volume; 2) the morbidity related to the normal tissue receiving 12Gy.

Methods: A retrospective review of 100 patients treated between 2004 and 2012 was performed. Giant AVMs (volume ≥ 15 cc) were excluded.

To delineate the target volume and the organs at risk, all patients had fusion of images between Angio-TC, Angio-MRI and a digital stereotactic angiography (DSA), the last two performed on the day of the treatment. The patients age ranged from 20 to 60 years old and were irradiated with a single dose fraction from 14-17Gy, using 6MV photon beam. The treatments were undertaken in Linear Accelerator 2300CD_Triology® (Varian Medical Systems, Inc., Palo Alto, CA), with the HD120 Micromultileaf incorporated, at Centro Oncológico Dr^a Natália Chaves, Carnaxide.

The first clinical evaluation was made one month post SRS. Imaging and clinical follow-up data were performed based on Angio-TC/MRI after 6, 12 months and yearly from then on. To assess the outcome, only patients with a minimum of 2 years of follow-up were included. Complete obliteration was always confirmed by DSA.

Results: 62.6% (N=57) of the patients had an excellent result with the complete obliteration of the AVM without any complication and 37.3% (N=34) of the patients have a major reduction of the nidus. 9% (N=9) of the patients were lost in follow-up. 47.2% of the patients showed complete obliteration after 2 years of follow-up, 5.5% more patients were cured after 3 years plus 4.4% and 5.5% after 4 years and 5 years respectively. The mean time to achieve complete obliteration was of 2.6 years.

Conclusion: The main temporary and permanent neurological sequelae are dose related to normal tissue irradiated, namely dose above 12Gy. The deficits found are dependent not only on the volume of the lesion, but also on the deep location of the irradiated brain.

#235

Dedicated linear accelerator radiosurgery for trigeminal neuralgia : a single-center experience in 238 patients with an anterior target.

Bertrand Debono (1), Igor Latorzeff (1), Yves Lazorthes (1), Jean-Albert Lotterie (1), Pierre-Yves Borius (1), Pierre Duthil (2), Isabelle Berry (1), Jean-Christophe Sol (1), Jean Sabatier (1)

1. Stereotactic Radiosurgery Unit, Toulouse University Hospital, Toulouse, France

2. Stereotactic Radiosurgery Hospital, Toulouse University Hospital, Toulouse, France

Introuction: Radiosurgery has been shown to be effective in treating trigeminal neuralgia (TN), with substantial advantages in safety and comfort. Few reports exist concerning TN treated using dedicated linear accelerator (LINAC)-based procedures. The authors evaluate the impact of this device with an anterior target (located on the plexus triangularis) on the rate of pain relief in patients with intractable TN undergoing stereotactic radiosurgery (SRS).

Methods: The authors conducted a retrospective review of 238 patients with idiopathic TN who were identified from a prospectively maintained database and were treated with BrainLAB Novalis LINAC system between May 2006 and June 2013. The median patient age was 69 years (range 38-106 years). All patients' pain was Barrow Neurological Institute (BNI) grades IV or V prior to treatment. Thirty patients (12,6%) had some sensory disturbance (usually paresthesias) preoperatively. Median duration of the TN was 7,2 years (range 1-39 years). Of these 238 patients, 67 (28%) underwent following various techniques for recurrent pain (percutaneous procedures, microvascular decompression). A team consisting of a neurosurgeon, a radiation oncologist, and a medical physicist performed dose selection and planning. A median dose of 85,6 Gy (75-90) was delivered on the anterior target in a noncoplanar archtherapy single-isocenter plan with a 6 mm circular collimator. The target was located on the nerve segment crossing the bony structure close to the plexus triangularis, and was delineated using MRI guidance fused with stereotactic CT scanning.

Results: The median follow-up was 33 months (range 4-82 months) ; 95 patients (40%) had > 3 years follow-up. At last check, 157 patients (65%) no longer had pain with or without treatment (BNI I and IIIa). A complete or significant improvement (BNI I to IIIb) was observed in 201 of 238 of patients (84,6%). Immediate failure was observed in 6 cases (2,5%). Recurrence was observed in 33 cases (13,8%, with average time: 31 months) and a new therapeutic procedure performed in 19 patients (8%), including 2 new SRS. Side effects were found in 47 patients (19,8%): 30 paresthesia (12,6%), 15 hypoesthesia 15 (6,3%), and severe neuropathic pain were observed in 2 patients (0,9%). The "target to nerve-emergence" distance was 12.3 mm (range 7.7 to 19.8 mm), and the "target-brainstem" distance was 7.2 mm (range 4.2 to 12.4 mm). The mean volume of brainstem receiving more than 10 Gy was lower than 0.1 cm³.

Conclusion: Despite a time-dependent deterioration in the success rate of dedicated-LINAC treatment for medically intractable TN, the study showed that Novalis LINAC and target are safe and effective alternatives treatment for trigeminal neuralgia, and are associated with a low rate of side effects. Long-term data, as those presented here, are important when counseling patients on their treatment options.

1.1.10 Experimental studies

#30

Deep Brain Stimulation of the anterior thalamic nucleus increases neurotrophin expression and neurogenesis in the rat dentate gyrus

Tharakeswari Selvakumar (1), Travis Tierney (1)

1. Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, United States

Introduction: High-frequency DBS of the anterior nucleus of the thalamus (ATN), a convergent node in the limbic circuit, is shown to have beneficial behavioral effects in patients with treatment-refractory epilepsy. The basic biological mechanism underlying the therapeutic effect of deep brain stimulation in this circuit is unknown. One possibility is that electrical stimulation of inputs to the hippocampus augments ongoing neurogenesis known to occur in the adult granular cell layer and that repopulation of the dentate gyrus reverses the deleterious effects of hippocampal degeneration.

Methods: We have found that high-frequency stimulation of the ATN in adult male Wistar rats elicits a wave of neurogenesis within the hippocampus. Electrically-induced neurogenesis may be mediated by trophic factors known to regulate neuron survival during neurodevelopment. Using quantitative PCR, we measured the expression levels of neurotrophic factors such as BDNF, NT4, FGF2 and other regulatory proteins in the rat hippocampus at 0, 3, 6, 12 and 24 hours after acute high-frequency stimulation of the anterior nucleus (2.5 V, 90 μ s, 130 Hz for 1 hour).

Results: We found that the expression level of these neurotrophic factors was increased significantly a few hours after DBS. Stereological cell counting revealed that the same electrical stimulation led to a 2.5 fold increase in neurogenesis in the dentate gyrus at five days after stimulation compared to sham controls. In addition, DBS also resulted in enhanced expression of GABA α 6 receptor subunit. GABA α receptors mediate inhibitory synaptic transmission in the central nervous and GABA receptor dysfunction is observed frequently in epilepsy. Another exciting recent finding is the down-regulation of the NMDA receptor subunit NR2C, post DBS surgery. Considering that NMDA receptor antagonists are used in epilepsy therapy, this observation expands our understanding about the mechanism behind the therapeutic benefits of DBS surgery.

Conclusion: Together these findings suggest that stimulation-dependent neurogenesis mediated by neurotrophic factors, enhanced GABA signaling and down-regulated glutamate signaling could contribute to the success of DBS in treating refractory epilepsy.

#54

Long-term Functional Recovery of Rodent Hemiparkinsonism by Carbon Nanotube-mediated siRNA 'Genetic Lesioning' of the Subthalamic Nucleus

Katie Bates (1), Marwan Hariz (2), Kostas Kostarelos (3)

1. *Nanomedicine Laboratory, Faculty of Life Sciences, University College London, London, United Kingdom*

2. *Unit of Functional Neurosurgery, Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, London, United Kingdom*

3. *Faculty of Medical & Human Sciences, University of Manchester, Manchester, United Kingdom*

Introduction: Since the dawn of functional neurosurgery for the treatment of Parkinson's disease in 1947 with the first stereotactic pallidotomy, the scene of functional neurosurgery has witnessed revolutionary developments to surgical procedures and astounding improvements in the treatment outcomes of patients. Combined with the shortfalls of pharmacological treatment strategies for Parkinson's Disease (PD) patients, resurgence in functional neurosurgery and the advent of more novel approaches are needed. This presentation will concentrate on nanotechnology as a platform for developing more effective and functional tools for neurosurgery.

Methods: One such type of nanomaterial platform for neurosurgery are carbon nanotubes (CNT). These are needle-shaped devices at the nanoscale with great potential for biomedical and clinical applications, mainly due to their capacity to pierce and translocate cell membranes. Chemically functionalised CNT complexed with small interfering ribonucleic acid (f-CNT:siRNA) constructs were stereotactically injected into the STN of 6-hydroxydopamine (6-OHDA) induced hemiparkinsonian rats with the aim to silence Bcl-2 expression and suppress pathological neuronal activity in the subthalamic nucleus (STN) by inducing localised apoptosis. Liposome:siRNA constructs were chosen as a clinically viable nanovector to which the biological efficacy, specificity and functionality of f-CNT:siRNA constructs were compared.

Results: Here we show superior biological activity of f-CNT:siRNA mediated gene silencing and functional recovery in hemiparkinsonian rats compared to liposome:siRNA treated animals. f-CNT:siRNA constructs were well-tolerated and afford long-term functional rehabilitation in hemiparkinsonian rats up to 12 weeks after administration.

Conclusion: We believe there is great potential in translational research incorporating nanotechnology that can have a great impact on the field of functional neurosurgery for the treatment of PD and other movement disorders.

#67

Kilohertz Frequency and Conventional Spinal Cord Stimulation in Rat Models of Different Pain Conditions

Björn Meyerson (1), Antti Pertovaara (2), Zhiyang Song (1), Hanna Viisanen (2), Bengt Linderöth (1)

1. Dept Clin Neuroscience, Karolinska Institutet, Stockholm, Sweden

2. Dept Physiology, Univ of Helsinki, Helsinki, Finland

Introduction: The objectives of the present study was to examine whether high frequency spinal cord stimulation (HF SCS), a new stimulation regimen since a few years focusing on the low back pain component in the so-called “failed back surgery syndrome” (FBSS), with subparesthetic intensity (similarly to the algorithm used clinically) is superior to conventional SCS in rat models of different types of pain. An additional aim was to elucidate the type of mechanisms behind the efficacy of HF SCS as compared to the conventional type by microrecordings of afferent activity in the dorsal column nuclei.

Methods: Rats were divided into various groups: one submitted to the spared nerve injury procedure (SNI) to create tactile hypersensitivity (“allodynia”); one submitted to acute nociceptive (pinch) pain and one to inflammatory pain after carrageenan injection into a hindpaw. All animals were tested for pain to normally innocuous tactile stimuli and nerve-lesioned animals also to pain in thermal tests. Normal healthy rats were used as controls. One group of nerve-lesioned rats was submitted to recording of afferent activity in the gracile nucleus (GN) during conventional 50 Hz and HF SCS at 10 kHz.

Results: HF SCS at either 500, 1000 or 10,000 Hz produced similar reductions of the allodynia after nerve lesion as did conventional SCS at 50 Hz but with slightly different time courses. A trial to rescue non-responders to conventional SCS with HF SCS was not successful. There was no significant difference in the effects of conventional and HF SCS in the acute pain model nor were there any differences in the SCS effects on inflammatory pain. Actually, 50 Hz SCS produced a slight but non-significant better effect in the heat and cold pain tests. Monitoring of activity in the dorsal column as projected to the GN showed, as expected, a massive activation by conventional SCS but no activation at all – and no inhibition of normal tactile transmission- during the HF SCS period (using subparesthetic amplitude).

Conclusion: In this study conventional SCS with (50 Hz; 200 usec and 80% of MT) proved similarly effective as HF SCS with subparesthetic amplitude in various pain models. The absence of conduction block of the dorsal columns with HF SCS fits well with the report that no sensory disturbance occur in the clinical studies. Since no activity is conveyed rostrally in HF SCS we hypothesize that the putative mechanisms of HF SCS are primarily segmental.

#123

Deep brain stimulation of the centromedian-parafascicular complex prevents apomorphine-, and attenuates dizocilpine-induced deficient sensorimotor gating in rats

Nadine Polascheck (1), Thomas Elle (1), Joachim K. Krauss (1), Kerstin Schwabe (1)
1. Neurosurgery department, Medizinische Hochschule Hannover, Hannover, Germany

Introduction: Here we investigated whether deep brain stimulation (DBS) of the rat centromedian-parafascicular complex (CM-Pf) improves deficient sensorimotor gating induced by either the dopamine-receptor agonist apomorphine, or the NMDA-receptor antagonist dizocilpine.

Deficient sensorimotor gating, measured as reduced prepulse inhibition (PPI) of the acoustic startle response, has been shown in subset of neuropsychiatric disorders, such as schizophrenia and Tourette's syndrome among others. PPI-deficits induced by apomorphine or dizocilpine in rats have been used as endophenotypes for certain symptoms in these disorders. We recently showed that stimulation of the CM-Pf, a target for DBS in Tourette's syndrome, improves breeding-induced deficient sensorimotor gating.

Methods: Electrodes were stereotactically implanted bilaterally in the CM-Pf of Sprague Dawley rats. After recovery from surgery, the rats were stimulated with 150 μ A (130 Hz and 160 μ s square wave pulse) or sham stimulated (without any current) for epochs of five days via a cable connected to the stimulator device. The effects of DBS on apomorphine- (vehicle and 1.0 mg/kg) or dizocilpine- (vehicle and 0.15 mg/kg) induced deficient PPI were tested on the last day of stimulation. Finally, the location of electrodes was histologically verified.

Results: CM-Pf DBS prevented the apomorphine-induced PPI-deficit, while dizocilpine-induced reduced PPI was alleviated. In vehicle-treated rats DBS had no effect on PPI.

Conclusion: This work indicates an important role of the CM-Pf for modulation of sensorimotor gating by the dopamine transmitter system, while the glutamatergic transmitter system seems to be less involved. Targeting the CM-Pf in apomorphine-induced deficient PPI may therefore be valuable to study the pathophysiology and the treatment of neuropsychiatric disorders with deficient sensorimotor gating such as schizophrenia or Tourette's syndrome. This model may also be used to further investigate the mechanisms of action of DBS in certain neuropsychiatric disorders.

#124

High frequency stimulation of the Subthalamic Nucleus improves graft survival and behavioural outcome in a rat model of Parkinson's disease

Luciano L Furlanetti (1), Joacir G Cordeiro (1), Karina K Cordeiro (1), Joanna AS Garcia (2), Christian Winkler (2), Guilherme Lepski (3), Volker A Coenen (1), Guido Nikkhah (4), Máté D Döbrössy (1)

1. Dept. of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Freiburg, Germany

2. Dept. of Neurology, Freiburg University Medical Center, Freiburg, Germany

3. Dept. of Neurology, University of São Paulo, Sao Paulo, Brazil

4. Dept. of Neurosurgery, University Hospital Erlangen, Erlangen, Germany

Introduction: Current surgical treatment for Parkinson's disease (PD) by neuromodulation of the subthalamic nucleus (STN) can temporarily improve motor symptoms. Alternative regenerative approaches are under research to reconstitute dopaminergic neurotransmission and offer a more extensive and long lasting repair. The aim of our project was to test whether the high frequency stimulation within the STN can act synergistically with dopaminergic grafts in reversing functional deficits.

Methods: Rats were rendered parkinsonian by unilateral injection of 6-OHDA into the right medial forebrain bundle (MFB). The MFB lesioned animals were assigned into two groups (STN-TX and TX-only). All animals were given striatal grafts of rat E14 ventral mesencephalic (VM) tissue into the ipsilateral striatum. Behavioral tests and post-mortem immunohistochemistry were performed.

Results: Survival of transplanted VM cells and functional recovery were observed in both transplanted groups, however the STN-TX group presented a significant increment in the number of grafted TH positive cells in comparison to the TX-only group. Furthermore, the stimulated and grafted group showed better outcome than the graft alone group in the Amphetamine-induced rotation test, in the Cylinder test, as well as in the Stepping test.

Conclusion: The read-outs as host re-innervation and behavioural recovery showed that dopaminergic grafts and DBS can act synergistically in the experimental model of PD. These findings suggest that cell therapy could be combined with STN neuromodulation. Further studies should be performed to confirm and extend these findings.

#125

Continuous and chronic bilateral deep brain stimulation of the medial forebrain bundle in rats

Luciano L Furlanetti (1), Máté D Döbrössy (1), Inigo Aguirre (1), Volker A Coenen (1)

1. Dept. of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Freiburg, Germany

Introduction: DBS for treatment-resistant major depressive disorder is an experimental option offering some patients a long-lasting control of the disease. Recently, bilateral DBS of the supero-lateral branch of the medial forebrain bundle (MFB) rapidly and dramatically reduced depressive symptoms in a clinical trial. However, chronic continuous bilateral high frequency stimulation (HFS) of the MFB has not been investigated experimentally.

Methods: Sprague-Dawley female rats (n=20) were submitted to bilateral stereotactic microelectrode implantation into the MFB. Chronic continuous HFS was applied for 3-6 weeks. Welfare monitoring and behavior changes were assessed. Post-mortem histological analysis of c-fos protein expression was carried out.

Results: MFB-HFS resulted in mild and temporary weight loss of 4-6% in the animals, but the weight was regained even with continuing stimulation. Exploratory motor activity increased during the initial 72 hours of stimulation, and food intake decreased by 25% up to 2 weeks post MFB-HFS. Stimulation did not influence performance on either a test of anxiety or behavioral despair. MFB-HFS led to increased and long lasting c-fos expression in the shell of the Nucleus Accumbens, the medial prefrontal cortex, the medio-dorsal thalamic nucleus and the lateral habenula.

Conclusion: Bilateral continuous chronic MFB-HFS is feasible and safe without impacting on the rodent's health. MFB-HFS results in temporary increase in exploration, which could explain the initial weight loss and decreased food intake. Chronic stimulation does not produce any apparent behavioral abnormalities. This platform represents a powerful tool for further preclinical investigation of the MFB stimulation in the treatment of depression.

#128

High-frequency stimulation of the Medial Forebrain Bundle reverses depressive-like behavior in a combined rodent model of depression and Parkinson's disease

Luciano L Furlanetti (1), Inigo Aguirre (1), Volker A Coenen (1), Máté D Döbrössy (1)

1. Dept. of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Freiburg, Germany

Introduction: Neuropsychiatric manifestations of Parkinson's disease (PD) have been associated to as much, if not more, morbidity as its classic motor features. A high prevalence of major depression in this population has been reported. HFS of the supero-lateral branch of the medial forebrain bundle (slMFB) has been proven in a recent clinical trial to provide in non-parkinsonian patients a prompt and consistent improvement of depressive symptoms. In order to better understand the underlying mechanisms of neuromodulation in the context of neuropsychiatric disorders, the effects of bilateral MFB-HFS were assessed in a combined rodent model of PD and depression.

Methods: Female Sprague-Dawley rats received unilateral 6-OHDA injection into the right MFB. Well-lesioned animals were selected for the experiment and fell into three groups: CMS/HFS, CMS/NO-HFS and Naïve control group (neither CMS, nor HFS). The CMS groups were submitted to a chronic mild stress (CMS) protocol for 6 weeks. MFB-HFS was applied only to the CMS/HFS group for 1 week. Over the experiment, all groups were repeatedly probed on a series of behavioral tasks to evaluate behavior changes following each intervention. Readouts of post-mortem histological analysis were also assessed.

Results: CMS led to an increase of immobility in the Forced-swim Test (FST), to a decrease of sucrose solution consumption in the Sucrose Preference Test (SPT), as well as to an increased production of ultrasonic vocalizations (USV) in the 22 kHz range. MFB-HFS completely reversed the anhedonic-like behavior evaluated in the SPT and vigorously abolished despair assessed in the FST. USV following stimulation showed a trend towards a decrement of 22 kHz accompanied by a simultaneous boost on 50 kHz emissions. MFB-HFS did not improve motor deficits associated to unilateral dorsostriatal dopamine depletion.

Conclusion: Our results suggest that unilateral dopamine depletion did not preclude MFB-HFS in reversing depressive-like and anhedonic-like behavior in a combined chronic rodent model of PD and depression. Further understanding of the importance of hemispheric dominance in neuropsychiatric disorders is essential in order to optimize stimulation as a therapeutic strategy in these diseases.

#129

Long-term characterization of the Flinders Sensitive Line rodent model of depression: Behavioral and PET evidence of a dysfunctional hippocampal system

Stephanie Thiele (1), Timo S Spehl (2), Lars Frings (2), Friederike Braun (2), Marisa Ferch (2), Philipp T Meyer (2), Luciano L Furlanetti (1), Volker A Coenen (1), Máté D Döbrössy (1)

1. Dept. of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Freiburg, Germany

2. Dept. of Nuclear Medicine, Freiburg University Medical Center, Freiburg, Germany

Introduction: Depression is one of the most common neurological diseases in the world affecting over 120 million people in the world. The aetiology of depression is unknown but key factors can include imbalanced neurotransmitter and neurotrophic factor levels, certain genetic mutations, as well as a hyperactive stress response. Diverse regions have been implicated in the pathology reflecting the characteristics of the network-model of depression that states that aspects of the syndrome can arise from dysregulation of neuronal activity at numerous loci on the limbic-cortical circuitry. The objective of the study was to evaluate regional brain glucose metabolism as a marker of neuronal dysfunction and the evolution of depressive-like symptoms in the Flinders Sensitive Line, a rodent model of depression.

Methods: The FSL rat has been selectively bred over 25 years to express depressive-like phenotype, mimicking various physiological and behavioural features of the disorder. However, there is limited understanding how these symptoms develop overtime in this model. In the current study we followed 11 FSL (6 females and 5 males) and 11 aged/ gender matched Sprague-Dawley rats over 8 months characterizing their performance at different time points on motor, sensorimotor and complex learning/memory based tasks. Using F18-FDG Positron Emission Tomography (PET), the rats cerebral metabolic activity was also compared to the matched controls by statistical parametric mapping (SPM) with a threshold of $p < 0.05$, uncorrected, > 20 contiguous voxels.

Results and conclusion: From the Early (2-3 months old) to the Late (6-7 months old) time points, the FSL animals lost their initial phenotype in the Elevated Plus Maze, and the Object Recognition Test. In the Forced Swim test, the FSL rats showed the tendency for increased immobility at both time points. Furthermore, the FSL animals showed a stable deficit on a learning and memory task, particularly indicating impairment in retention of spatial information. The PET scan at 3 months of age showed bilateral, left dominant decrease in glucose metabolism in the entorhinal cortex in the FSL rats

#159

Conceptualization and validation of an open source closed-loop deep brain stimulation system in rats

Hemmings Wu (1), Hartwin Ghekiere (2), Dorien Beeckmans (1), Tim Tambuyzer (2), Kris van Kuyck (1), Jean-Marie Aerts (2), Bart Nuttin (3)

1. *Research Group Experimental Neurosurgery and Neuroanatomy, KU Leuven, Leuven, Belgium*

2. *M3-BIORES: Measure, Model & Manage Bioresponses, Department of Biosystems, KU Leuven, Leuven, Belgium*

3. *Department of Neurosurgery, University Hospitals Leuven, KU Leuven, Leuven, Belgium*

Introduction: Conventional deep brain stimulation (DBS) technique applies constant electrical stimulation to specific brain regions to treat neurological disorders. Closed-loop DBS with real-time feedback is gaining attention in recent years after proved more effective than conventional DBS in terms of pathological symptom control clinically. Here we demonstrate the conceptualization and validation of a closed-loop DBS system using open source hardware in rats.

Methods: We used hippocampal theta oscillations as system input, and electrical stimulation in the mesencephalic reticular formation (mRt) as controller output. It is well documented that hippocampal theta oscillations are highly related to locomotion, while electrical stimulation in the mRt induces freezing. We implemented Arduino, an open source microcontroller, between input and output.

Results: This allowed us to use hippocampal local field potentials to steer electrical stimulation in the mRt, which significantly suppressed locomotion compared to baseline based on real-time hippocampal theta monitoring and corresponding mRt stimulation. The advantages of open source hardware include wide range of selection and availability, and high customizability.

Conclusion: Our open source closed-loop DBS system proves to be robust and reliable, and provides researchers an alternative solution to preclinical closed-loop neuromodulation.

#178

Efficacy of rostral and caudal PPN stimulation in an experimental rat model for Parkinson's disease based on the functional STN-PPN connectivity.

Marcus Janssen (1), Filipa Campos (2), Joao Casaca-Carreira (3), Ali Jahanshahi (3), Sarah Heschem (4), Graca Baltazar (5), Nuno Sousa (2), Yasin Temel (6)

1. Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands

2. Life and Health Sciences Research Institute (ICVS), University of Minho, Braga, Portugal

3. Department of Neuroscience, Maastricht University, Maastricht, The Netherlands

4. Department of Neuroscience, Maastricht University, Maastricht, The Netherlands

5. Department of Medical Sciences, University of Beira Interior, Covilhã, Portugal

6. Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands

Introduction: Parkinson's disease is a neurodegenerative disorder with progressive motor symptoms. Motor symptoms are tremor, bradykinesia, rigidity and disturbed gait. Initial motor symptoms respond well to dopamine replacement therapies. Also DBS of the STN has proven to be an effective treatment. On the long term, patients experience more gait disturbances. Current, drug and surgical therapies are however not effective to treat these axial symptoms. DBS of the PPN is promising; though the optimal target still needs to be defined. Here, we investigated the effects of PPN DBS on gait in a rat model of PD

Methods: First the functional STN-PPN connectivity was investigated by the neuronal cell activation in the PPN induced by stimulation of the STN with a frequency of 60 and 130 Hz. Thereafter the effects of DBS in the rostral and caudal region of the PPN in a rat model of PD on gait were assessed. For this purpose rats were trained to cross the CatWalk to evaluate the effect of DBS on gait changes induced by bilateral dopamine depletion. In addition, we assessed general motor performance and anxiety-like behavior

Results: Both low and high frequency stimulation induced c-Fos activation in the PPN. The number of c-Fos positive cells was significantly higher in the rostral compared to the caudal part of the PPN. Bilateral 6-OHDA injections in the medial forebrain bundle resulted in a significant reduction of TH positive cells. In 6-OHDA treated animals the swing duration was increased and swing speed and general speed was reduced. Also a trend was seen in the reduction of the stride length. DBS of the PPN reversed these changes. Stimulation of the posterior part seemed to be more effective. No differences were found in STN c-Fos activation between anterior and posterior PPN stimulation

Conclusion: The functional STN connectivity seems to be strongest with the anterior part of the PPN. On the contrary, DBS of the posterior part of the PPN seems to have better effect on gait changes in a bilateral 6-OHDA rat model for PD. Anterior and posterior PPN stimulation resulted in the same amount of c-Fos activated cells in the PPN. Therefore it can be hypothesized that the effects of PPN stimulation on gait in PD are not related to the PPN-STN-basal ganglia network. It is well possible that these stimulation effects are related to the PPN-cerebellar network.

#192

Striatal and entopeduncular nucleus single neuronal discharges and oscillatory activity in the 6-OHDA rat model of Parkinson's disease with levodopa-induced dyskinesia

Xingxing Jin (1), Kerstin Schwabe (1), Joachim K Krauss (1), Mesbah Alam (1)
1. Department of Neurosurgery, Hannover Medical School, Hannover, Germany

Introduction: This study investigates the neuronal firing characteristics and oscillatory activities of the striatum and entopeduncular nucleus (EPN) in the 6-OHDA rat model of Parkinson's disease (PD) with and without L-DOPA- induced dyskinesia (LID). The nigrostriatal loss of dopamine leads to hypokinesia together with excessive oscillatory beta band activity within the basal ganglia-cortical loop, while enhanced theta band activity is related to LID.

Methods: Twelve 6-OHDA lesioned hemiparkinsonian (HP) rats, eight of which were rendered dyskinetic by repeated injection of L-DOPA (HP-LID) were used. Single unit activity and local field potentials were measured in urethane (1.2 g/kg, i.p) anesthesia in the dorsolateral striatum and the EPN by platinum-tungsten microelectrodes "off" and after L-DOPA injection "on". Motorcortex activity was measured by an electrocorticogram.

Results: Firing activity in the striatum and EPN was similar in HP-LID and HP rats. Injection of L-DOPA decreased the firing rate in both groups in the EPN, without affecting the striatal firing rate. Striatal oscillatory activity in the theta band (4-8 Hz) was higher in HP-LID rats in both, "on" and "off" state as compared to HP rats. In the EPN theta activity did not differ between groups, but decreased in the "on" state in both groups. In both regions the beta activity (12-30 Hz) was higher in HP rats as compared to HP-LID rats in the "off" state, L-DOPA injection, however, reduced beta activity to a larger extent in HP-LID rats as compared to HP rats.

Conclusion: The findings of this study indicate that LID is associated with increased theta oscillatory activity in the striato-cortical loop of basal ganglia.

#199

Delta oscillations in the bed nucleus of the stria terminalis correlate with compulsion in a rat model of obsessive-compulsive disorder

Hemmings Wu (1), Tim Tambuyzer (2), Ioana Nica (3), Kris van Kuyck (1), Jean-Marie Aerts (2), Sabine Van Huffel (4), Bart Nuttin (5)

1. Research Group Experimental Neurosurgery and Neuroanatomy, KU Leuven, Leuven, Belgium

2. M3-BIORES: Measure, Model & Manage Bioresponses, Department of Biosystems, KU Leuven, Leuven, Belgium

3. M3-BIORES: Measure, Model & Manage Bioresponse, Department of Biosystems, KU Leuven, Leuven, Belgium

4. Department of Electrical Engineering (ESAT), Division SCD, KU Leuven, Leuven, Belgium

5. Department of Neurosurgery, University Hospitals Leuven, KU Leuven, Leuven, Belgium

Introduction: Elevated anxiety level and dysfunctional reward circuitry are important contributors to clinical symptoms of obsessive-compulsive disorder (OCD). The bed nucleus of the stria terminalis (BNST) is implicated in both anxiety and reward processing. Specific neuronal groups in the BNST related to anxiety and reward have been identified, but quantitative data about the information carried by local field potential (LFP) signals in this area during obsession/compulsion is lacking. We hypothesised that LFPs in the BNST were correlated with compulsive behaviour in an animal model of OCD.

Methods: We recorded LFPs in the BNST and other random brain regions during compulsive and non-compulsive behaviours in 32 Wistar rats, and performed time-frequency analysis.

Results: Our data showed that the relative power of delta band began to increase before compulsion, peaked during compulsion, and decreased after compulsion stopped. These correlations were not found in the same group of rats before they developed compulsion, not in random control brain regions in rats exhibiting similar compulsive behavior, nor in the BNST in control rats. The percentage change of BNST delta power from before to during compulsion, and from during to after compulsion, also correlated with the ameliorating effect on compulsion during BNST high-frequency electrical stimulation, further confirming the link between BNST delta power and compulsion.

Conclusion: These results warrant further assessments of the use of LFP for closed-loop neuromodulation in psychiatric indications.

#276

The hyper direct pathway in the basal ganglia is the location of 5-HT_{2C} and D2 receptors interaction and controls the emergence of purposeless oral movements.

Mélanie Lagièrre; Marion Bosc; Philippe De Deurwaerdère

University Of Bordeaux, Bordeaux, France

Introduction: Excessive dopamine (DA) transmission in associative/limbic areas of basal ganglia is thought to underline a variety of behavioral disorders including dyskinesia. The excessive DA tone promotes alterations on other neurochemical pathways and numerous authors have suggested that serotonergic (5-HT) controls, notably via the 5-HT_{2C} receptor, are triggered in case of DA changes. The possible locations of the interaction between DA transmission and 5-HT_{2C} receptors within basal ganglia are not known.

Methods: Here, we studied in Sprague-Dawley male rats the contribution of 5-HT_{2C} receptors using the 5-HT_{2C} antagonist SB243213 in the effects elicited by the dopaminergic D₂ agonist quinpirole on both purposeless oral movements, c-Fos expression in basal ganglia nuclei and the electrophysiological activity of substantia nigra *pars reticulata* (SNr) neurons, the main output of basal ganglia, responding to the electrical stimulation of the cingulate cortex.

Results: The results showed that SB243213 (1mg/kg i.p.), without effect by itself, blocked the purposeless oral movements induced by 0.5 mg/kg i.p. quinpirole. The levels of the protein c-Fos, barely affected by quinpirole or SB-243213, were significantly increased in the subthalamic nucleus (STN) when the treatments were combined. Interestingly, in urethane-anesthetized rats, the effect elicited by the electrical stimulation of the cingulate cortex (700 µA; 0.3 Hz), characterized by an excitatory-inhibitory-excitatory response in a small population of SNr neurons, was subtly changed by the drugs. Quinpirole did enhance the amplitude of the early excitatory response (+80% compared to saline-treated rats), involving the hyper direct pathway and the STN, and the 5-HT_{2C}-receptor antagonist abolished this effect.

Conclusion: These results extend previous evidence that excessive DA tone triggers 5-HT_{2C} receptors-dependent controls in basal ganglia. The interaction occurs likely on the hyper direct pathway in line with the role of the STN in mediating the purposeless oral movements induced by DA and 5-HT_{2C} agonists. Our study shows that 5-HT_{2C} antagonisms could be therapeutically relevant in limiting abnormal motor behaviors triggered by DA agonists and highlight the predominant role of the STN, in particular through the hyper direct pathway, in the control of movement disorders.

1.1.11 Brain-Machine Interface

#35

A WIRELESS CORTICAL PROSTHESIS FOR EPILEPSY AND BCI

Pantaleo Romanelli (1), Napoléon Torres Martinez (2), Alim Louis Benabid (3)

1. *Neuroscience, AB Medica, Milano, Italy*

2. *Clinattec, CEA LETI, Grenoble, France*

3. *Functional Neurosurgery, Clinattech, Grenoble, France*

Introduction: A wireless low-profile cortical prosthesis was implanted on a non-human primate to provide chronic cortical monitoring and stimulation. High quality ECoG signals have been obtained daily for 6 months from the 16 contacts thin-layer cortical grid. Impedance values, recorded daily as well on each contact, remained very low for the entire duration of the experiment. Brain function mapping was performed on a monthly base using direct cortical stimulation and recording somatosensory evoked potentials.

Methods: ECOGIW-16E is a compact low-profile device integrating an RF antenna and a flexible thin-film Neuronexus grid (thickness 15 micron) bearing 16 platinum electrodes. A custom-made monkey cage equipped with RF coils was developed to allow seamless recharging of the implanted device. ECOGIW-16E was implanted in a male macaque monkey (*Macaca fascicularis*, 6.95 kg). Experimental protocol was approved by the regional committee (Cometh Grenoble number 12/136_Clinattec-NTM-01). The animal was anesthetized and secured to a stereotaxic frame. Image-guided craniotomy was performed, placing the 16 contacts grid over the left sensorimotor cortex (M1-S1) after intraoperative cortical mapping.

Results: Post-surgical recovery was very fast: the monkey woke up shortly after the procedure and resumed his regular activities within a few hours. Due to the low profile design, the device could not be identified by visual inspection of the monkey's head. High quality ECoG signals have been recorded 3 to 4 times a week over the 16 contacts for 6 months. Daily impedance values remained constantly under 30 kOhms for all the 16 contacts. Hand and finger movements could be elicited through remotely-guided wireless cortical stimulation, which was performed on a monthly base. We were able to record and analyze median and tibial nerve Somato-sensorial evoked potentials (SSEP) in an anesthetized primate. Using easily recognizable features (maximal negative and positive peak and phase reversal) in the SSEP, we identified the location of motor cortex confidently during the observation period. Inversely, a reduction in amplitude in the first peak of SSEP was seen in all electrodes during the 6 month period. The device was removed, under general anesthesia, after 6 months. No sign of fibrosis or adherence between the grid and the underlying brain was found on macroscopic inspection. Histology is underway.

Conclusion: ECOGIW-16E is a wireless chronically implantable cortical prosthesis providing an optimal medium for BCI and epilepsy surgery (enhancing seizure focus localization but also providing cortical stimulation).

#82

Reliable control of a brain-machine interface using epidural electrocorticography

Jocelyne Bloch (1), Ricardo Chavarriaga (2), Aleksander Sobolewski (2), Robert Leeb (3), Etienne Pralong (4), José del R. Millán (3)

1. Neurosurgery, CHUV, Lausanne, Switzerland

2. Defitech Chair in Non-Invasive Brain-Machine Interface Center for Neuroprosthetics, EPFL, Lausanne, Switzerland

3. Defitech Chair in Non-Invasive Brain-Machine Interface Center for Neuroprosthetics, EPFL, Lausanne, Switzerland

4. Neurosurgery, CHUV, Lausanne, Switzerland

Introduction: Recent advances in brain-machine interfaces (BMI) have shown how these devices are able to decode neural activity in real time to control neuroprosthetic devices, e.g. to restore motor capabilities. Currently most of these systems rely on signals recorded using electrodes implanted intra-cortically or subdural electrocorticography (ECoG) arrays. In contrast, epidural electrodes over motor cortex are commonly used for stimulation to alleviate neuropathic pain, but seldom used for recording brain activity. This work shows how field potentials recorded with epidural ECoG over the motor cortex of a patient were used to successfully control a brain-machine interface over several days.

Methods: A 50 year-old male patient suffered a left brachial plexus avulsion 30 years before the time of the surgery, followed by a complete upper limb plegia and hypoesthesia. He progressively developed a deafferentation pain. After a positive antalgic response to rTMS of the right motor cortex, an epidural electrical motor cortex stimulation was proposed. Preoperatively, a functional MRI showed an atrophic but functional right "hand knob". Two Resmed Medtronic electrodes were implanted above central sulcus on the primary motor and sensory cortex contralateral to the plegic hand. Intraoperative electrophysiological confirmation of electrode contacts' location was performed using direct motor response of the shoulder and the face to contact stimulation. Contact leads were externalized for 9 days and used to decode cortical activity during (attempted) motor tasks. Five experimental sessions were performed (1, 3, 4, 8 and 9 days after the operation). The subject sat in front of a computer screen showing 5 gray circles arranged to form a cross. At the beginning of each trial a cursor was placed at the central circle and the subject was asked to attempt moving his plegic hand as if controlling the cursor with a mouse towards one of the peripheral circles (i.e. forward, backward, left and right directions) and then back to the central position. Given the complete paralysis of the hand, no actual movement was produced. At each trial the target location was cued by changing the circle color to red; after 2s the circle changed color to orange, and - after another 2 s - to green prompting the subject to start the attempted movement (GO cue). Each session lasted less than 2 hours and yield about 80 trials. Stimulation was ceased during these sessions and ECoG signals were recorded using a g.Tec g.USBamp acquisition system at a sampling rate of 512 Hz (8 channels corresponding to the 2 implanted leads; reference and ground electrodes were placed at mastoid). Data was processed in real time by extracting the spectral power in frequency bands of 2Hz in the range of 2-40 Hz. Data from the first day was used to train an initial classifier to discriminate between resting and movement periods of the plegic hand. From the second day on, the classifier output was used to control the movement of the cursor. This classifier was updated after each recording session using the data collected up to that point.

Results: We identified discriminant movement-related modulations of cortical activity in the mu-band (8-12 Hz) under most electrodes. This activity was highly specific, allowing consistent recognition of onset of attempted movements in all trials. At the same time it yielded less than 6% rate of false. Real-time decoding of these signals enabled control of the cursor with a median response time of about 1.2s after the GO cue. Importantly, classifiers were trained on the data of previous days without any recalibration on the same day. This suggests that the selected features are highly reliable and stable across days.

Conclusion: Here we demonstrate that neural activity recorded from the motor cortex using epidural electrodes can successfully be used to control a BMI device.

Remarkably good performance was achieved across days in a hemiplegic patient even though several decades have passed since the time of the lesion. These results support the idea that this approach can constitute a less invasive, safer alternative to recording techniques currently used for brain-machine interfacing.

#83

Neuronal expression of c-Fos after epicortical and intracortical electric stimulation of the primary visual cortex

Belal Neyazi (1), Makoto Nakamura (2)

1. *Departement of Neurosurgery, KRH Nordstadt, Hannover Medical School, Hannover, Germany*

2. *Department of Neurosurgery, Hannover Medical School, Hannover, Germany*

Introduction: The goal of our study was to evaluate the topographical differences of neuronal activation after electrical stimulation over the primary visual cortex compared to intracortical stimulation in layer IV by using different intensity of currents with constant high frequency 10Hz stimulation.

Electrical stimulation of the primary visual cortex is an experimental approach for visual prostheses. We here compared the response to intracortical and epicortical stimulation of the primary visual cortex by using c-Fos immunoreactivity as a marker for neuronal activation.

Methods: The primary visual cortex of male Sprague Dawley rats was unilaterally stimulated for four hours using bipolar electrodes placed either intracortically in layer IV (n=26) or epicortically (n=20). Four different current intensities with a constant pulse width of 200 μ s and a constant frequency of 10Hz were used, for intracortical stimulation with an intensity of 0 μ A (sham-stimulation), 10 μ A, 20 μ A and 40 μ A, and for epicortical stimulation 0 μ A, 400 μ A, 600 μ A and 800 μ A. Subsequently all animals underwent c-Fos immunostaining and c-Fos expression was assessed in layer I-VI of the primary visual cortex within 200 μ m and 400 μ m distance to the stimulation site.

Results: C-Fos expression was higher after intracortical stimulation compared to epicortical stimulation, even though ten times lower current intensities were applied. Furthermore intracortical stimulation resulted in more focal neuronal activation than epicortical stimulation. C-Fos expression was highest after intracortical stimulation with 20 μ A compared to all other intensities. Epicortical stimulation showed a linear increase of c-Fos expression with the highest expression at 800 μ A. Sham stimulation showed similar expression of c-Fos in both hemispheres, the contra-lateral hemisphere was not affected by intracortical or epicortical stimulation of either intensities.

Conclusion: In summary, intracortical stimulation resulted in more focal neuronal activation with less current than epicortical stimulation.

#255

Reconstruction of Upper Limb Movement from Electrocorticographic Signals to Control Functional Electrical Stimulation for Hand Function Restoration

Omid Talakoub (1), Cesar Marquez-Chin (2), Wong Willy (3), Jessie Navarro (4), Clement Hamani (5), Erich Fonoff (4), Milos R Popovic (6)

1. *Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Canada*

2. *Rehabilitation Engineering Laboratory, Toronto Rehabilitation Institute, University Health Network, Toronto, Canada*

3. *Electrical and Computer Engineering, University of Toronto, Toronto, Canada*

4. *Department of Neurology, University of Sao Paulo, Sao Paulo, Brazil*

5. *Toronto Western Research Institute, University Health Network, University of Toronto, Toronto, Canada*

6. *Rehabilitation Engineering Laboratory, Toronto Rehabilitation Institute, University Health Network, Toronto, Canada*

Introduction: A Brain-Machine Interface (BMI) is a technology that decodes brain signals and transforms them into control signals to drive an electronic device. Operation of this technology does not require the user to generate any muscle activity. As a result, BMI technology holds enormous potential to be used as an assistive device for individuals with little or no ability to perform voluntary movements. An important application of BMI is the extraction of kinematic information of voluntary movement from neural signals. With this ability, it could be possible to control a neuroprosthetic device to restore movements and provide an unprecedented level of transparency in the control of the assistive device; users of this technology could simply attempt performing a movement, and the prosthetic or neuroprosthetic device would respond accordingly.

Methods: We explored the possibility of identifying upper limb movement kinematics using two standard four-contact subdural electrodes placed over the primary motor cortex. Using eight contacts dramatically simplifies the BMI design and makes the system more feasible from engineering and clinical perspectives. Electrocorticography (ECoG) is a method for recording the electrical activity of the brain using subdural electrodes. ECoG signals are generally accepted as having a wider bandwidth and higher spatial resolution than electroencephalographic (EEG) recordings. ECoG has a number of advantages when compared to single neuron or other deep brain recording techniques. We showed in our earlier study that amplitude of ECoG recording after temporal alignment resembles arm velocity in reaching tasks. In the current study, we hypothesize that the amplitude ECoG recordings from primary motor cortex is proportional to arm speed. We employ a Multi-Linear Regression (MLR) model to quantify relationship between neural activity and kinematic data. Multi-linear regression model describes how hand velocity can be reconstructed from linear combination of ECoG recordings. Linear operations are not computationally expensive and can be used in a real-time system. The arm kinematic is not simply driven from linear combination of ECoG recordings because MLR does not take into consideration two important physiological characteristics of the motor system. The first is the delay between the cortical activity and the corresponding motor output. The lag represents a transmission delay between cortical motoneuron spike response and emergence of EMG/kinematic activity, and consists of conduction time in the corticospinal tract, relay in the spinal cord, conduction in motor axons and then the neuromuscular junction. We incorporate the delay into the linear model as a fitting parameter. The second physiological characteristic relates to event-related power changes in the beta and gamma frequency bands. These events are reliable indicators of the starting and stopping of arm movements. We desire the predicted output to be "gated" (i.e. turned on or off) by the activity in the beta and gamma bands. Specifically, high activity in beta band coupled with low energy in gamma band is an indicator of the cessation of movement and vice versa.

Results: Leave-one-out cross-validation is used for assessing the accuracy of the proposed model. The average Pearson correlation between the estimated velocity and actual limb velocity was exceeding 80% even though placement and choice of number of implanted ECoG contacts were dictated by clinical requirements. To date, very few studies have addressed the issue of predicting complex movement trajectories from human ECoG data. These studies yielded an average correlation of approximately 50% for arm trajectory despite having good electrode coverage across the entire motor cortex.

Conclusion: Our simple prediction model shows the possibility of designing a real-time brain machine interface to restore movement in individuals with paralyzed limb through neurprosthetic devices such as functional electrical stimulation (FES). Consequently, users are not limited to pre-defined reaching or grasping movements but rather they can reach to any object within close proximity of their body. This system could be used as a movement assistive device by individuals with chronic motor and sensory impairments. Moreover, combination of BMI and FES may have therapeutic effect for individuals with limited movement impairment such as stroke survivors or individuals with incomplete spinal cord injury.

1.2 Abstracts selected for Flash Oral Presentations

1.2.1 Movement disorders

#13

Suboptimal benefits of subthalamic stimulation in elderly Parkinson's disease patients

Mr Chiou Shang-Ming (1)
1. Taiwan

Introduction: Deep brain stimulation (DBS) of subthalamic nucleus (STN) is an accepted treatment for drug-refractory Parkinson's disease (PD). However, there is general reluctance to consider this therapy for patients aged 70 years or older. This study delineated the age impacts on STN-DBS outcomes in PD patients.

Methods: Seventy-two consecutive patients were divided into younger and elderly groups (cutoff age=70 years). Absolute changes in the daily levodopa-equivalent dose (LED) and in drug-off/DBS-on Unified PD Rating Scale (UPDRS) scores after 6-months relative to those of presurgical drug-off baseline were evaluated in both groups. Preoperative factors predictive of favorable surgical outcomes were analyzed using multivariate linear regression.

Results: Before surgery, both groups were matched in clinical severity. Absolute reductions in daily LED and dyskinesia indicated nonsignificant intergroup differences. Elderly patients exhibited lower surgical improvements, particularly the UPDRS Part II ($P<0.05$), than younger patients did. A higher preoperative baseline UPDRS motor score was predictive of motor improvement at 6-months in younger patients ($P<0.001$, Adjusted $R^2=0.496$). Elderly patients achieved a significant improvement if they presented dominantly with akinesia before surgery ($P<0.001$, Adjusted $R^2=0.657$).

Conclusion: STN-DBS therapy is safe and beneficial to elderly PD patients. However, its clinical effectiveness was inferior in elderly patients compared to that in younger patients.

#19

Deep brain stimulation in complex tremor

Ersoy Kocabicak (1), Dursun Aygun (2), Murat Terzi (2), Musa Onar (2), Hatice Guz (3), Omer Boke (3), Yasin Temel (4)

1. Department of Neurosurgery, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

2. Department of Neurology, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

3. Department of Psychiatry, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

4. Departments of Neuroscience and Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

Introduction: Deep brain stimulation (DBS) is accepted as the gold standard treatment method in medically refractory essential tremor. However, clinical results of DBS in multiple sclerosis, head trauma, ischemia or intracerebral surgery related tremor is still controversial. We present the clinical results of complex tremor cases who had DBS in our clinic in light of the literature.

Case descriptions: Case 1: 37-year-old female patient with medically refractory, multiple sclerosis related, right upper extremity dominant tremor provoked by posture and movement with high amplitude, 7-10 Hz frequency and FahnTolosa Marin tremor scale score (FTMTS) of 72. The patient underwent bilateral thalamic Vim-Vop DBS with microelectrode recording (MER). FTMTS score improved 50% at first year follow-up.

Case 2: 29-year-old female patient with right upper extremity dominant Holmes tremor following a severe head trauma with a frequency of 4-5 Hz, mini mental test score (MMSE) of 29 and FTMTS of 72. The patient underwent unilateral thalamic Vim-Vop DBS with microelectrode recording (MER). FTMTS score improved 29% at first year follow-up.

Case 3: 70-year-old male patient with essential tremor for 50 years with increased sound and head tremor refractory to treatment, FTMS: 76, sound and head tremor 3/4 and 2/4 respectively. The patient underwent bilateral thalamic Vim-zona incerta DBS with microelectrode recording (MER). FTMTS score improved 61% at first year follow-up. Sound and head tremor regressed to 1/4 and 0/4 respectively.

Conclusion: There are publications in the literature concerning that DBS is generally less effective in complex tremor cases compared with essential tremor or Parkinson's disease tremor. Our limited case results are in line with the literature. These lesions are thought to be the results of compromise in the cerebellorubrothalamic tract in different levels in different ways.

#27

The impact of deep brain stimulation on tinnitus: a multicenter questionnaire study

Jasper V Smit (1), Marcus LF Janssen (2), Malou Engelhard (1), Rob MA De Bie (3), Arne Mosch (4), Fiorella Contarino (4), Robert J Stokroos (1), Yasin Temel (5)

1. *Department of Ear Nose and Throat/Head and Neck Surgery, Maastricht University Medical Center, Maastricht, Netherlands*

2. *Department of Neurology, Maastricht University Medical Center, Maastricht, Netherlands*

3. *Department of Neurology, Academic Medical Center, Amsterdam, Netherlands*

4. *Department of Neurology, HagaHospital, The Hague, Netherlands*

5. *Maastricht University Medical Center, Department of Neurosurgery, Maastricht, Netherlands*

Submitter: Mr Smit Jasper (NL)

Introduction: Deep brain stimulation (DBS) has recently gained interest in the treatment of tinnitus. However, not many targets have been assessed on the effect of stimulation on tinnitus. Therefore, we conducted a multicenter questionnaire study in a large cohort of patients who received DBS in a broad spectrum of targets for various indications.

Methods: All patients that underwent DBS surgery in the Academic Hospital Maastricht, Amsterdam Medical Center and HagaHospital (The Hague) were included in this study (n=685). The first part of the questionnaire consisted of questions about the situation before DBS and the second part consisted of questions informing about the current situation. Control patients with solely tinnitus were matched in a matched subject design. Both parts of the questionnaire included visual analogue scale (VAS) loudness, VAS burden and tinnitus handicap inventory (THI).

Results: The THI decreased significantly during DBS compared to the situation prior to surgery (from 18.9 to 15.1, $p<.000$), which was only significant for DBS in the subthalamic nucleus (STN). The THI in the control group (36.9 to 35.5, $p=.546$) and other DBS targets did not change. The VAS loudness increased in the control group (5.4 to 6.0 $p=.004$). The incidence of newly formed tinnitus following DBS was 10.5%, which is almost twice as high as reported in literature.

Conclusion: DBS might have a modulatory effect on pre-existing tinnitus and, in other cases, gives rise to generation of new phantom sounds. In this questionnaire, STN DBS has the best effects on tinnitus, but most likely other nuclei linked to the tinnitus circuitry might be even more effective.

#28

Infections associated with deep brain stimulators: Characteristics and Outcome

David Bervini (1), Stefano Giulieri (2), Trampuz Andrej (3), Claudio Pollo (4), Marc Levivier (1), Jocelyne Bloch (1)

1. Neurosurgery, Lausanne University Hospital, Lausanne, Switzerland

2. Infectious Diseases, Lausanne University Hospital, Lausanne, Switzerland

3. Septic Surgery Unit, Charite, University Medicine Berlin, Berlin, Germany

4. Neurosurgery, Bern University Hospital, Bern, Switzerland

Submitter: Mr Bervini David (CH)

Introduction: Treatment of deep brain stimulator (DBS) infections is not standardized. Complete device removal with delayed reimplantation is generally recommended. Partial or complete retention combined with debridement and antimicrobial treatment against biofilms is an attractive alternative, but data on the outcome are lacking. We analyzed DBS-associated infections treated in our institution.

Methods: All DBS revisions for infection performed in a single institution over a 13-year period (Jan 2001-Feb 2014) were retrospectively reviewed. DBS-associated infection was diagnosed if a sinus tract communicating with the device was present or if local signs of infection (redness, swelling, secretion) were associated with positive deep cultures (≥ 2 positive samples were required for low virulent organisms).

Results: 239 consecutive cases underwent DBS implantation. A total of 11 cases of DBS-associated infections were identified, of which 10 (4.2%; 95%CI: 2.2-7.6%) occurred after implantation in our institution and 1 elsewhere. In 9 cases of infection, DBS was implanted for treatment of Parkinson's disease, while a patient with Lesch Nyhan syndrome experienced 2 distinct bilateral DBS infections. Infection occurred after a median of 167 days after implantation (range, 10-4678) and 78 days after last revision (range, 3-266). The causative pathogens were identified in 10 cases including *S. aureus* ($n = 8$), *P. acnes* ($n = 1$) and mixed infection in 1 case (*S. marcescens* and *S. aureus*). As initial procedure, intracranial device retention was performed in 9 cases (5 partial and 4 complete); removal of the whole device was performed in 2 cases. Median duration of antibiotic treatment was 40 days (range, 14-168 days), 7 cases received rifampin-containing regimens. After a median of 22 months after completion of treatment, 8 cases (72.3%) showed no signs of infection, 2 patients had a relapse of the extracranial component of the device 225 and 820 days after completion of antibiotic treatment and 1 patient had persistent infection. All 3 failures were treated with removal of the device. Rifampin-resistant *S. aureus* was cultivated in 2 cases of failure.

Conclusion: DBS-associated infection was observed in 4.2% of implanted devices with *S. aureus* as the predominant pathogen. Debridement and device retention was performed in 9 of 11 cases, of which 3 developed a relapse or persistent infection. The role of device retention and rifampin in the treatment of DBS-associated infections needs further investigations.

#40

Can the substantia nigra pars reticulata be stimulated by the electrode in subthalamic nucleus stimulation?

Takashi Kawasaki (1), Yuiko Kimura (2), Masahiro Shin (1), Makoto Taniguchi (1), Fusako Yokochi (3), Ryoichi Okiyama (3), Yshitomo Umitsu (4), Hironobu Tokuno (4), Seki Erika (5), Nobutaka Arai (5)

1. *neurosurgery, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan*

2. *Neurosurgery, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan*

3. *neurology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan*

4. *Brain structure, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan*

5. *Laboratory of Neuropathology, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan*

Introduction: Recently, some reports have described attempts to stimulate the substantia nigra pars reticulata (SNr) for freezing gait and balance disturbances in patients with advanced Parkinson's disease. The electrode tip in patients who received deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been assumed to be located at the STN/SNr border, and the intention has been to stimulate the SNr using these electrodes. Amelioration of gait and balance disturbance can be expected by SNr stimulation, since projections to the pedunculopontine nucleus (mesencephalic locomotion center) extend from the SNr. However, while the presumption is that the electrode tip is definitely located in the SNr, studies have merely shown the location of the electrode tip by superimposing data from postoperative magnetic resonance imaging (MRI) on an atlas. Whether the tip of the electrode was actually in the SNr thus remains unclear. To clarify this issue, we investigated distributions of the pars reticulata and pars compacta (SNc) within the substantia nigra (SN).

Methods: Serial frozen sections (thickness, 50 μ m) were prepared using three formalin-fixed human brains. Kluver-Barrera-stained slices were made every 500 μ m. These slices were observed under microscopy, and the SNr and SNc were identified. We also composed 3-dimensional images of the SN on the computer from these slices, and drew the trajectory of the STN-DBS electrode onto these images. We then clarified whether the tips were located in the SNr or SNc.

Results: Distributions of the SNc and SNr were revealed as follows. The SNc exists in the SNr as speckles of complicated-looking islands, with a tendency for the SNc to be mediodorsal and the SNr to be lateral and medioventral. Considerable individual differences were also apparent between the three brains. The 3D images showed that electrode tips were not only in the SNr, but also in the SNc. Moreover, the tip in the SNr was located very close to the SNc. The tips of the STN-DBS electrodes are thus not always located within the SNr, and current could spread to the adjacent SNc if the SNr is stimulated successfully.

Conclusion: Several reports have described possibilities for psychiatric symptoms by substantia nigra stimulation. Ensuring that the SNr is stimulated is important if effects on freezing gait are to be ensured. Determining the location of the electrode tip using postoperative MRI superimposed on an atlas is inadequate. We investigated where the tips of STN-DBS electrodes were located. These tips were not only in the SNr, but also in the SNc. Clinical studies aimed at showing effects of the SNr-DBS must confirm both that the electrode tip is within the SNr using microelectrode recordings and that adverse effects do not arise in intraoperative test stimulations.

#42

Decline in verbal fluency after subthalamic nucleus deep brain stimulation in Parkinson's disease : a lesional effect of the electrode trajectory ?

Stéphane Derrey (1), Floriane Travers (2), Romain Lefaucheur (2), Vianney Gilard (1), David Maltete (2)

1. Neurosurgery, Rouen University Hospital, Rouen, France

2. Neurology, Rouen University Hospital, Rouen, France

Introduction: Decline in verbal fluency (VF) is the most consistent neuropsychological adverse effect reported after deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson disease (PD). We investigated whether the decline in VF is correlated with a lesional effect of the electrode pathway from the cortical entry point to the STN target.

Methods: We retrospectively analysed 59 PD patients (mean age, 61.9 years old; mean disease duration, 13 years) who underwent bilateral STN-DBS in our center from 2007 to 2013. VF tests were performed before surgery and 6 months after. For semantic and phonemic VF, patients were categorized into two groups: decline and stable group. The electrode pathway was determined thanks to the fusion of preoperative MRI with postoperative CT-scan. For each trajectory, 6 points of interest were studied: the lateral and antero-posterior angles, the intersection with the caudate, thalamic or pallidus nuclei and the distance through the STN.

Results: A significant decline of VF, both in semantic and phonemic tasks, was found after surgery, respectively 14.9% ($p < 0.001$) and 14.2% ($p < 0.001$). For semantic VF (44 decline patients and 15 stable), for the left trajectory, i) the antero-posterior angle was significantly higher ($p = 0.03$) in the stable group (60.1°) than in the decline group (56°) and ii) the intersection with the thalamus was more frequently observed in the stable ($n = 17$) than the decline group ($n = 10$) ($p = 0.03$). For phonemic VF (44 decline patients, 15 stable patients), no significant difference was observed between decline and stable group for the trajectory.

Conclusion: Decline in semantic VF may be partially caused by a lesional effect on the left trajectory with a more anterior cortical entry point than in the stable group. Inversely, a trajectory passing through the left thalamus was safer for VF. This may suggest the role of the dorso-lateral prefrontal cortex and/or the anterior arm of the internal capsule in the decline of semantic VF.

#47

The in vivo application accuracy of the neuromate® robot during frame based stereotactic implantations of electrodes for DBS

Daniel Von Langsdorff (1), Marco Sgambati (1), Philippe Paquis (1), Denys Fontaine (1)
1. Neurosurgery, Hôpital Pasteur, Nice, France

Introduction: The Neuromate neurosurgical robot is routinely used for the implantation of DBS electrodes. Its in vitro application accuracy has been evaluated but not the accuracy for DBS under in vivo conditions. With an independent system of measurement, we evaluated the in vivo application accuracy of the Neuromate robot during electrodes implantations for frame-based DBS procedures.

Methods: The target was defined on the robots' dedicated targeting software (Voxim). The theoretical stereotactic coordinates calculated by this software were compared with the coordinates reached intraoperatively by the tip of the tube guides using x-rays in combination with the Stereoplan localizer system. The Euclidian distance between the point theoretically targeted by the robot and the point reached by the tube guide was calculated, based on their respective stereotactic coordinates. This procedure was first experimented in vitro with the stereotactic frame fixed on the robot without patient, for 21 points widely distributed in the stereotactic space. The in vivo accuracy was then evaluated in 40 basal ganglia targets in 23 consecutive patients undergoing DBS for movement disorders.

Results: In vitro the mean application accuracy (SD) was 0,44 mm (0,23 mm). The maximal localization error was 1,0 mm. In vivo the mean application accuracy (SD) was 0,85 mm (0,28 mm); mean $\Delta x = 0,34$ mm (0,30) ; mean $\Delta y = 0,34$ mm (0,26) ; mean $\Delta z = 0,58$ mm (0,29). The maximal error was 1,55 mm.

Conclusion: The Neuromate neurosurgical robots' in vivo application accuracy in frame-based DBS procedures, and measured with a system independent from the robot, was more precise than one millimeter. This accuracy is compatible with the accuracy required in DBS procedures and is at least similar to the accuracy of stereotactic frame arms.

#48

The effect of dopaminergic therapy on intraoperative microelectrode recordings for subthalamic deep brain stimulation under GA: can we operate on patients in the 'ON' state?

M. J. Asha (1), H. Krovvidi (2), J. Kausar (1), C. Shirley (3), H. Pall (4), R.D. Mitchell (1)

1. Neurosurgery, Queen Elizabeth Hospital, Birmingham, United Kingdom

2. Neuroanaesthesia, Queen Elizabeth Hospital, Birmingham, United Kingdom

3. Neurophysiology, Queen Elizabeth Hospital, Birmingham, United Kingdom

4. School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, United Kingdom

Introduction: Microelectrode recording (MER) plays an important role in target refinement in deep brain stimulation (DBS) of the subthalamic nucleus (STN) for Parkinson's disease (PD). Traditionally, patients were operated on in the 'off medication' state to allow intra-operative assessment of patient's response to direct STN stimulation. With the introduction of DBS under general anaesthesia (GA), the need for intra-operative stimulation has become unnecessary. However, the routine withdrawal of dopaminergic medications has remained. This retrospective review examines the effect of continuing these medications on intraoperative MER for subthalamic DBS insertion under GA and discusses the clinical implication of this approach.

Methods: A retrospective review of PD patients who had bilateral STN DBS insertion identified a cohort of 7 patients (14 STN DBS insertions) between (2012-2013) who accidentally underwent the procedure while 'on medication'. This 'ON' group was compared to all other patients who underwent the same procedure, within the same period, and had their medications withdrawn preoperatively, the 'OFF' group, n=26 (52 STN DBS). The primary endpoint was defined as the number of microelectrode tracks required to obtain STN specific MER's. A second end point was the length of MER's that was finally used to guide the DBS lead insertion.

Results: The 'ON' and the 'OFF' groups were statistically comparable in all baseline characteristics including: age at operation (49 years (33-52) vs 52 years (29-66) , $p=0.28$), duration of disease (10 (6-20) vs 11 (6-21) years, $p=0.96$), gender F:M ratio (1:6 vs 9:17, $p=0.40$). Both groups had similar PD medications regimes preoperatively expressed as L-Dopa Equivalent Daily Dose (LEDD), 744 mg/day (525-3591) compared to 1000 mg/day (366-3265) , $p=0.77$.

Satisfactory STN recording was obtained via single track in both hemispheres in all 7 patients in the 'ON' group (100%) compared to 15 patients only on the 'OFF' group (57.7%), $p=0.067$. The length of STN recording was 4.5 (3.0 – 5.5) mm in the 'ON' group compared to 3.5 (2.9 – 4.5) mm in the 'OFF' group, $p=0.17$.

Conclusion: STN DBS insertion under GA can be performed without the need to withdraw dopaminergic treatment preoperatively. In this review the continuation of medications did not affect the physiological localisation of the STN.

#50

Bilateral ablative surgery for Parkinson's disease

Kostiantyn Kostyuk (1), Vitaliy Tsymbaliuk (2), Yurii Medvedev (1), Andriy Popov (1), Maksym Shevelov (1), Valeriy Cheburakhin (1), Sergei Dichko (1)

1. Functional neurosurgery, Institute of neurosurgery, Kyiv, Ukraine

2. Restorative neurosurgery, Institute of neurosurgery, Kyiv, Ukraine

Introduction: Parkinson's disease (PD) is one of the most widespread progressive neurodegenerative diseases, which in most cases has bilateral clinical signs. Since the middle of 20th century ablation surgical interventions play a prominent role in the treatment of PD. In spite of wide use of neuromodulation technology during the last decades, the application of lesion procedures remain important in the treatment of extrapyramidal hyperkinesia, in view of economical, geographical and some other reasons. The problem of bilateral ablative surgery for PD stays debated because of high risk of postoperative complications. The purpose of the study is to evaluate the effectiveness of bilateral stereotactic lesion procedures for PD.

Methods: During the period of 2008 -2013, 455 patients with PD underwent ablative surgery, among them 20 (4.4%) had bilateral lesions. 14 (3.1%) patients underwent thalamotomy with contralateral pallidotomy and 6 (1.3%) patients underwent thalamotomy with contralateral subthalamotomy. Surgery performed on CRW Stereotactic system using StereoPlan, StereoAtlas (Radionics) and Frailink (Medtronic) softwares. During surgery macrostimulation was used to delineate the optimal target location. Neuropsychological status was assessed by: UPDRS II, Hoehn and Yahr scale, Schwab and England scale, MMSE. Postoperative follow-up was from 6 months to 5 years (mean 2.1 ± 0.4 years).

Results: Patients' age ranged from 50 to 2 years (mean – 60.7 ± 1.8 years). The mean duration of disease before surgery was 10.2 ± 1.1 years. 16 from 20 patients (80.0%) used L-dopa therapy from 3 to 12 years (mean – 4.8 ± 1.8 years), 8 (40.0%) of them had motor fluctuations and 2 (10.0%) – had levodopa-induced dyskinesia. Period between surgeries ranged from 1.5 to 6.5 years (mean 3.4 ± 0.45 years). In 1 year after the second intervention UPDRS score improved by 54.4% in ON period and by 43.8% in OFF period. Levodopa-induced dyskinesia stopped after surgery in both patients who had it before treatment. The dose of levodopa decreased on the average on 31.3% - from 854.7 ± 343.0 mg/day to 583.3 ± 257.4 mg/day. Complications were observed in 4 (20.0%) cases. After pallidotomy 3 patients developed focal neurological deficit, in 1 of them – permanent (dysarthria - in 2 cases and contralateral hemiparesis – in 1 case). In 1 patient after subthalamotomy developed lesion-induced hemiballism, which regressed in 7 months after surgery.

Conclusion: Our results demonstrate that bilateral ablative surgery is an effective and safe method of treatment for PD. Such treatment improves overall motor function, increases patient's mobility, daily living activities and improves quality of life. Bilateral lesion interventions allow patients to reduce levodopa dose providing them with increased freedom from a complex medication regimen. Deep brain stimulation offers the advantage when compared to classic ablative surgery. At the same time lesion interventions may be the best options on some occasions, especially for patients in the developing countries, where medical care has not sufficient support from public institutions. The technical and science progress permit to perform more precise stereotactic lesion interventions for getting reliable and safe results. Careful identification and selection of patients for ablative surgery allow to achieve sophisticated results in treatment of PD.

#71

A susceptibility-weighted MRI-based analysis of the subthalamic nucleus footprint in patients with Parkinson's disease and non-Parkinson's disease controls and electrophysiological validation of the morphology

James McEvoy (1), Ismail Ughratdar (2), Stefan Schwarz (3), Dorothee Auer (3), Surajit Basu (4)

1. Department of Neurosurgery, University of Nottingham Medical School, Nottingham, United Kingdom

2. Department of Neurosurgery, Nottingham University Hospitals, Nottingham, United Kingdom

3. Department of Academic Radiology, University of Nottingham Medical School, Nottingham, United Kingdom

4. Department of Neurosurgery, Nottingham University Hospitals, University of Nottingham, Nottingham, United Kingdom

Introduction: Advancements in MRI have allowed neurosurgeons to use direct targeting of the subthalamic nucleus (STN) for planning of deep brain stimulation (DBS) surgery. Recently susceptibility-weighted imaging (SWI) was found to generate higher contrast between the STN and its surroundings. SWI uses variation in magnetic tissue susceptibility and is influenced by iron content of the tissue. In PD the iron content of nigral cells increases. However neurophysiological validation of SWI -STN has not been done before which will allow surgeons to use this sequence for direct target selection. Aim: To compare SWI STN morphology in Parkinson's disease (PD) patients and non-PD controls and to validate SWI STN morphology by use of microelectrode recording (MER).

Methods: Preoperative SWI sequences of 7 PD patients (14 STN) undergoing DBS surgery over a 12 months period were reviewed and compared with 7 non-PD controls (3 dystonia, 4 healthy volunteers, totalling 14 STN). Mean coordinates for STN medial, lateral and apex were compared between groups using t-tests. Area of STN footprint (mm²) was also compared. Intraoperative MER data identifying electrophysiological STN-SNR boundary was then correlated with SWI predicted STN-SNR margin.

Results: Our results show that SWI-predicted STN-SNR boundary can be accurately correlated to electrophysiological boundary in 85% of the MER trajectories. The STN footprint in PD patients was similar to non PD subjects, however subgroup analysis showed that the STN footprint in PD is significantly bigger compared to dystonia patients 11.05mm² compared to 7.69mm². Mean lateral coordinate of STN for PD patients in this study was 13.32, with a range of 11.32 to 15.48 (+/- 1.28), the vertical reach had a mean of -0.07 with a range of -3.15 to +1.73 and depth was -5.64 (+/- 1.02) from the AC -PC plane. Hence SWI demonstrated a bigger STN footprint than the accepted atlas description, which is proved to be electrophysiologically valid. The clinical outcome showed more than 50% improvement in UPDRS score in all the above PD patients.

Conclusion: Our study showed that SWI-STN matches with electrophysiological STN validated by intraoperative MER recordings in awake patients. SWI STN footprint is larger than the conventional atlas described STN. Direct targeting using SWI images is safe for clinical application.

#75

A prospective, randomized assessment of GPi and/or Voa-Vop DBS in a case of stroke induced hemidystonia

Philipp J Slotty (1), Walleed Dabbas (1), Christopher R Honey (1)
1. Division of Neurosurgery, Vancouver General Hospital, Vancouver, BC, Canada

Introduction: In primary and generalized dystonia the internal pallidum (GPi) is the most common target for deep brain stimulation (DBS) and provides good to excellent results in the majority of patients. Our results in secondary dystonia due to stroke have not been as good and prompted a search for additional DBS targets. The thalamus (Voa-Vop) has been lesioned with success in dystonia and we therefore undertook a study to compare the outcome of GPi DBS versus Voa-Vop DBS versus both in the following patient.

Methods: Three years after suffering a left sided putaminal stroke due to a heart aneurysm at the age of six, the patient developed a right sided hemidystonia. At age 22 left sided Voa-Vop and GPi DBS were implanted in a single surgical procedure. Programming was blinded to the patient and examiner and each possible combination of stimulation (GPi only, Voa-Vop only, GPi and Voa-Vop) was tested. After 3 months of stimulation in each setting the BFMDRS, GNDS (disability scale) and SF-36 (quality of life) were completed.

Results: Simultaneous GPi and Voa-Vop stimulation was preferred by the patient and resulted in the best functional improvement measured by the BFMDRS and GNDS and the highest improvement in quality of life as measured by the SF-36.

Voa-Vop or GPi stimulation alone slightly improved QoL and was felt by the patient to be subjectively better than their baseline but did not result in improvement of dystonic movement rated by the BFMDRS.

Conclusion: Simultaneous thalamic and pallidal DBS proved to be the most effective therapy for this patient suffering from secondary hemidystonia due to a putaminal stroke. Multi-target DBS should be considered for post-stroke dystonia and may offer improved outcome in other forms of secondary dystonia with limited response to GPi DBS.

#77

Predictive factors of cognitive outcome in PD patients treated with Stn-DBs and medical therapy

Clarissa Cavandoli (1), Andrea Trezza (1), Alberto Bona (1), Manuela Pilleri (2), Angelo Antonini (3), Erik Sganzerla (1), Andrea Landi (1)

1. Neurosurgery, San Gerardo Hospital, Monza, Italy

2. Neurology, IRCCS San Camillo, Venezia, Italy

3. Neurology, IRCCS San Camillo, Venezia, Italy

Introduction: Deep Brain Stimulation of Subthalamic Nucleus (STN-DBS) is an effective therapy for advanced Parkinson's disease (PD), however it is debatable if DBS might provoke cognitive deficits. Dementia rate after DBS ranges from 6-30% and the prevalence of Mild Cognitive Impairment (MCI) ranges from 3 to 28% after 3 year follow up in published papers. The expected rate of dementia in patients treated with pharmacological therapy is lower. There is no agreement about demographic and clinical factors, which may condition cognitive outcome. Nevertheless preoperative cognitive status and brain atrophy have been indicated as possible predicting factors of DBS cognitive outcome. This study was aimed to assess progression of cognitive decline and incidence of MCI and dementia in PD patients treated with STN-DBS compared with a population of pharmacologically treated patients and to determine whether preoperative cognitive status or specific pattern of brain atrophy could affect cognitive outcome.

Methods: 26 consecutive patients were included in this study. 13 underwent STN-DBS and 13 followed pharmacological therapy (PHT). All the patients were evaluated before treatment with CAPSIT protocol and full neuropsychological tests. Follow up was performed after 1 year. At basal evaluation and follow up the patients were classified as: cognitive preserved, with mild cognitive impairment (MCI) and demented, according to international criteria, on the base of cognitive performances. In the DBS cohort, preoperative 1.5-Tesla MRI (T1 W) was acquired to analyse the cortical thickness.

Results and conclusion: At basal evaluation the prevalence of MCI was similar in the DBS and PHT groups and none presented dementia; prevalence of MCI and dementia did not significantly differ at follow up in the two cohorts. Patients classified as MCI at basal evaluation had increased risk to develop dementia at follow up independently from the treatment (DBS or PHT). At a preliminary analysis, no correlations were found between cortical thickness and cognitive outcome in the DBS cohort.

#81

Deep brain stimulation of STN for advanced Parkinson disease with octopolar leads: Programming electrical parameters guided for a neuroanatomical-3D-image software

Muñoz Jorge (1), Gabriel Salazar (2), Cladellas Josep Maria (3), Tardaguila Manel (1)

1. Neurosurgery, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain

2. Neurology, Neurology-unit of movement disorders, Barcelona Parkinson-Hospital Terrassa CST, Terrassa, Barcelona, Barcelona, Spain., Barcelona, Spain

3. Neurosurgery, Hoapital Universitari Germans Trias i Pujol, Barcelona, Spain

Introduction: Deep brain stimulation of bilateral sub-thalamic nucleus (DBS-STN) is a secure and effective neurosurgical technique to ameliorate the cardinal parkinsonian symptoms and the complications associated to the chronic use of L-dopa. The tetrapolar leads commonly used for DBS show limited possibilities to control the different symptoms (motor and non-motor) that can show Parkinson Disease (PD) patients. There are few effective guides to optimize the electrophysiological parameters after lead's implantation in DBS-STN. The objective of this presentation is to demonstrate our experience in DBS-STN in four advanced PD patients with octopolar leads and guided for a 3D neuroanatomical software. We describe DBS-STN in four advanced and complicated PD patients using octopolar leads and describe the usefulness of a 3D-Visual neuroanatomical guidance after lead implantation.

Methods: Four advanced PD patients were subjected to bilateral STN-DBS, Octopolar leads were implanted in the STN regions with multiple independent current control (MICC) technology. A Cranial MRI and one week post surgery CT images were fused and inserted in a 3D-neuro-anatomical-visual software (GUIDE, BSC), the electrophysiological parameters were established guided for the fused cranial images. Common PD scales were collected Basal and 6 weeks and 12 weeks post surgery.

Results: DBS-STN bilateral using octopolar leads was effective and secure in our PD patients described here. They improved motor fluctuations, non motor symptoms and QOL objectified in Usual PD scales.

Conclusion: Octopolar lead, combined with MICC, could bring more possibilities to stimulate different STN regions in advanced PD patients with different motor and non motor symptoms. GUIDE (BSC) could be useful to optimize the electrophysiological parameters in advanced PD patients

#89

Taste disturbances in thalamic deep brain stimulation - analysis of a common therapeutic dilemma

Bastian Sajonz (1), Burkhard Mädler (1), Stephan Herberhold (2), Sebastian Paus (3), Niels Allert (4), Volker Arnd Coenen (1)

1. Department of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Freiburg, Germany

2. Department of Otolaryngology, Bonn University Medical Center, Bonn, Germany

3. Department of Neurology, Bonn University Medical Center, Bonn, Germany

4. Movement Disorders Clinic, Neurological Rehab Center "Godeshoehe", Bonn, Germany

Submitter: Mr Coenen Volker Arnd (DE)

Introduction: Stimulation-induced taste disturbances in thalamic deep brain stimulation (Vim-DBS) have been addressed in two case reports so far. However, an inquiry among 16 patients with VIM-DBS revealed that half of them suffered from stimulation-induced taste disturbances. Using tractography we want to analyse this apparently common phenomenon, including patients with bi- and multipolar stimulation settings. We postulate that the distance between the volume of activated tissue and the gustatory tract determines the occurrence of stimulation-induced hypogeusia.

Methods: Using preoperative DTI and the postoperative helical cranial computed tomography, effective electrode positions were determined in relation to the medial lemnisci (ML) and the dentato-rubro-thalamic tracts (DRT). The surrounding volume of activated tissue (VAT) was calculated from stimulation settings. The distance between the VAT and the medial margin of the ipsilateral ML was measured (DeltaVAT-LM). Tremor improvement under Vim-DBS was assessed with the Essential Tremor Rating Scale (ETRS). Ten patients took part in an otolaryngologic examination including subjective gustometry with deactivated, unilateral left and right stimulation, respectively, as well as bilateral stimulation. Gustometry scores were calculated to determine stimulation-induced changes in gustation.

Results: Eight out of sixteen patients reported stimulation induced hypogeusia. Left and right DeltaVAT-LM were significantly shorter in patients with subjective stimulation-induced taste disturbances. There was a significant positive rank correlation between mean DeltaVAT-LM of each patient and the gustometry score. There was no correlation between tremor improvement on the ETRS and the gustometry scores.

Conclusion: Although rarely reported stimulation induced taste disturbances seem to be a common rather than an exceptional therapeutic dilemma in Vim-DBS. Corroborating our hypothesis shorter values of DeltaVAT-LM result in stimulation induced hypogeusia. The exact course of the gustatory tract cannot be defined by tractography due to its small volume. However, a medial juxtaposition with the ML at the target of Vim-DBS can be inferred. So DeltaVAT-LM is used as a substitute for the distance between the VAT and the gustatory tract. Good tremor control is not associated with taste disturbances. In fact, individual fiber anatomy with a converging point of the DRT as the stimulation target and the assumed course of the gustatory tract at the stimulation site seems to be the cause of stimulation induced hypogeusia.

#95

Pallidal and nucleus accumbens stimulation in Tourette Syndrome: a four cases series report

Paweł Sokal (1), Marek Harat (1), Marcin Rudas (1), Marcin Rusinek (1)
1. Neurosurgery, Military Research Hospital, Bydgoszcz, Poland

Introduction: Gilles de la Tourette Syndrome (GTS) can be successfully treated with deep brain stimulation (DBS). There is no consensus upon which target in DBS guarantees the best outcome. Objective: We wanted to evaluate the effects of DBS in four patients treated with bilateral DBS.

Methods: 4 patients with GTS were treated with bilateral DBS in Department of Neurosurgery of Military Research Hospital in Bydgoszcz, Poland in years 2012-2013. 3 patients (males, 36y, 23y, 19y) with internal globus pallidus (GPi) DBS and 1 patient (male, 19y) with nucleus accumbens (NAc) DBS. Outcome was assessed based on the number of vocal and motor tics with follow-up ranging 12-24 months.

Results: In patients with GPi DBS we observed reduction of 50%, 30%, 60%, respectively, in vocal tics and 60%, 90%, 40% in motor tics. In the 4th patient with NAc DBS the effect was 40% reduction of vocal tics and 90% reduction of motor tics.

Conclusion: Reduction of symptoms of GTS in patients treated with GPi or NAc DBS after 1 or 2 years is satisfactory for patients and their families and significantly helps people to overcome this chronic disorder. Based on our experience DBS in GTS is highly recommended in our opinion.

#103

Frameless system (nexframe) in deep brain stimulation. Study of accuracy comparing neurophysiological and electrodes coordinates

M. Mondani (1), S. D'Auria (1), M. Skrap (1), R. Eleopra (2), C. Lettieri (2), S. Rinaldo (2),

1. Neurosurgical department, S. Maria della Misericordia hospital, Udine, Italy

2. Neurological department, S. Maria della Misericordia hospital, Udine, Italy

Introduction: Stereotactic systems are traditionally used in order to get the right target in deep brain stimulation (DBS). Recently, 3 tesla MRI is able to recognize the targets directly. The elaboration of these images on the neuronavigator allowed implantation of the electrode using a frameless technique (Nexframe, Medtronic) in spite of the traditional frame. In a consecutive series of 66 patients, delivery of electrodes had been done without frame. All patients underwent 3T MRI in order to visualize target and trajectory. Comparing stereotactical coordinates of neurophysiological target with those of more distal contact of final electrodes, we wanted to confirm the range deviation of the system.

Methods: We present a series of 66 patients operated from January 2010 until January 2013. Median age is 55,26 years. There are 40 males and 26 females. We treated 21 patients with generalised dystonic syndrome, 41 with Parkinson's disease, 2 with essential tremor and 2 with epilepsy.

Surgical planning has been done through 3T-MRI fused with axial tomography. The targets were subthalamic nucleus (STN) for Parkinson's disease, ventroposterolateral part of internal pallidum (GPI-VPL) for dystonia, Anterior Nucleus of thalamus for epilepsy (ANT) and Ventrointermediate Nucleus (Vim) for essential tremor. We used simultaneous multitracking microrecording. All electrodes have been locked on the skull with the stimlock system. All dystonic patients received a rechargeable system. Electrode position has been postoperatively confirmed by axial tomography, fused with preoperative MRI. There were no major complications. Once fused postopCT and preopMRI, variation from the expected neurophysiological coordinates were figured out.

Results and conclusion: Frameless system (Nexframe, Medtronic) is a technique guided directly by the image, it means that we can directly visualize the nuclei on 3T-MRI and reach them with a navigation system. It is more comfortable, less invasive and less time consuming, which may compensate the cost of the material. There are a few data about lacking of precision through any step of the procedure: firstly anatomical stereotactic coordinates, neurophysiological stereotactic coordinates and finally stereotactic coordinates of the tip of the electrode.

Analysis of vectorial error in three dimension, gave a mean vectorial error of 1.41 mm. Comparing what we found with literature, this value is ranging with tolerability of framebased system.

Therefore, with regard to our experience and based on postoperative studies, this data confirms the same reliability and precision of the frame. We think that Nexframe with image guided surgery is a good alternative of stereotactic frame in DBS surgery.

#112

Deep brain stimulation of the Globus Pallidus internus for Holmes tremor

Rachel Martinez (1), William Omar Contreras Lopez (2), Marcus Pinsker (3), Thomas Reithmeier (4), Erich Talamoni Fonoff (5), Luciano Furlanetti (6), Oscar Escobar (7), Gabriel J Arango (8)

1. *Functional and Stereotactic Department, University of Sao Paulo Medical School, Sao Paulo, Brazil*

2. *Functional and Stereotactic Department, University of Sao Paulo, Sao Paulo, Brazil*

3. *Functional Neurosurgery, Berlin Helios Kliniken, Berlin, Germany*

4. *Neurosurgery, Munchen University, Freiburg, Germany*

5. *Functional and Stereotactic Neurosurgery, University of Sao Paulo, Sao Paulo, Brazil*

6. *Functional and Stereotactic Neurosurgery, Freiburg University Clinic, Freiburg, Germany*

7. *Functional Neurosurgery, CIMAD, Bogota, Colombia*

8. *Neurology, CIMAD, Bogota, Colombia*

Introduction: Holmes tremor (HT) is a resting, postural and kinetic, irregular low frequency (<4.5 Hz) symptomatic tremor, caused by a lesion in the brainstem, thalamus or cerebellum. Chronic deep brain stimulation (DBS) of the nucleus ventralis intermedius (VIM) has been explored as a surgical treatment due to unsatisfactory pharmacological outcomes. Notwithstanding, VIM stimulation is not always possible due to secondary structural disruptions of thalamic anatomical structures and its connections. In search for other alternatives, this article analyses the efficacy of globus pallidus pars internus (Gpi) DBS for the treatment of HT.

Methods: We studied 10 patients submitted to DBS for the treatment of HT from March 2002 to June 2012. The first targeted option was the Gpi nucleus; seven patients received Gpi DBS, while three patients unresponsive to intraoperative Gpi stimulation received VIM DBS. Fahn-Tolosa-Marin tremor rating scale (TRS) was used to evaluate outcome.

Results: In all observed cases we observed an improvement on the Tremor-Rating-Scale after DBS (according to TRS) one postural-tremor case achieved the maximum possible tremor-reduction (from 4 to 0 points, meaning 100% tremor- reduction), in the 9 resting-tremor-cases the average reduction was of 3 points (or 75%). The average improvement in the intention-tremor group (10 cases) was of 2 points (or 50%) and the results were sustained at 2 years follow-up.

Conclusion: The present data suggests that chronic stimulation of Gpi nucleus may induce sustained control of Holmes tremor, especially of the resting component. Gpi stimulation could be considered as an alternative target for cases in which thalamic anatomy is considerably altered.

#115

Neurosurgical treatment in dystonia: A proposed algorithm and its outcome in a case series of 80 patients

Jairo Alberto Martinez Espinoza (1), William Omar Contreras Lopez (2), Marcus Pinsker (3), Gabriel J Arango (4), Xiomara Garcia (5), Luciano Furlanetti (6), Inigo Aguirre (7), Jorge Humberto Marin (8), Oscar Escobar (9)

1. *Functional and Stereotactic Department, University of Sao Paulo Medical School, Sao Paulo, Brazil*

2. *Functional and Stereotactic Department, University of Sao Paulo, Sao Paulo, Brazil*

3. *Functional Neurosurgery, Berlin Helios Kliniken, Berlin, Germany*

4. *Neurology, CIMAD, Bogota, Colombia*

5. *Neurology, Department of Stereotactic and Functional Neurosurgery, Movement Disorders and Pain Clinic – CIMAD, Bogota, Colombia*

6. *Functional and Stereotactic Neurosurgery, Freiburg University Clinic, Freiburg, Germany*

7. *Molecular Neurosurgery, Institut des Neurosciences Cellulaires et Intégratives (INCI) CNRS/Université Louis Pasteur de Strasbourg, Strasbourg, France*

8. *Neuroradiology, Hospital San Jose, Bogota, Colombia*

9. *Functional Neurosurgery, CIMAD, Bogota, Colombia*

Introduction: In this study, we assessed the outcomes of patients with dystonia who had undergone surgery. Likewise a treatment algorithm for Dystonia is proposed by the SLANFE.

Methods: Eighty consecutive patients with dystonia received neurosurgical management by means of intrathecal pump implantation, pallidotomy or deep brain stimulation (GPi or VIM). These patients included 48 patients with primary dystonia and 32 patients with secondary dystonia. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) was used to access pre- and post-operative outcomes. Patients were follow-up for a minimum of 12 and up to 114 months.

Results: The mean improvement in BFMDRS among patients with PrD was 87.54%, and the mean improvement in BFMDRS among patients with SeD was 42.21%. Hemidystonic patients in both groups (PrD, SeD) showed a mean improvement in BFMDRS of 71.05% with GPi DBS. Patients with SeD due to previous perinatal insults showed a mean improvement in BFMDRS of 41.9%, with better results in purely dyskinetic patients (mean improvement of 61.2% in BFMDRS).

Conclusion: Using the proposed algorithm facilitated surgical decision planning, which translated in improved diagnostic rates, earlier interventions, appropriate management plans and outcomes for both groups (PrD, SeD). However, neuroimaging findings had a positive prognostic significance in the response to treatment in patients with primary dystonia compared with patients with secondary dystonia or distortion of basal ganglia anatomy.

#143

Bacterial biofilm formation on neurostimulation systems

Bujung Hong (1), Andreas Winkel (2), Mahmoud Abdallat (1), Assel Saryyeva (1), Götz Lütjens (1), Meike Stiesch (2), Joachim K Krauss (1)

1. Department of Neurosurgery, Hannover Medical School, Hannover, Germany

2. Department of Prosthetic Dentistry and Biomedical Material Science, Hannover Medical School, Hannover, Germany

Submitter: Mr Hong Bujung (DE)

Introduction: Bacterial biofilm formation on the surface of any implanted device may be associated with infection close to the implants necessitating device removal. The aim of this study is to identify specifically the DNA of bacterial biofilm on neurostimulation systems using polymerase chain reaction (PCR).

Methods: Forty-five pacemakers were aseptically removed during routine surgery for battery replacement in 36 patients with implanted neurostimulation systems. The devices were stored immediately at -80°C under sterile conditions. To determine the presence of bacterial, the pacemakers were processed and DNA was extracted. 500-bp fragments of purified DNA were amplified using universal primers which target hypervariable regions within the bacterial 16S rRNA gene. In the following Single Strain Conformation Polymorphism (SSCP) analysis, genetic information of different bacterial species were separated from each other, isolated, re-amplified, and finally identified using sequencing methods.

Results: On the surface of 3 pacemakers (deep brain stimulator, n=2; occipital nerve stimulator, n=1), which were collected from 3 patients (mean age, 42 years) PCR detected DNA of gram-positive bacterial. The specimens were derived from staphylococcus epidermidis (n=1), lactobacillus iners et crispatus (n=1), and bacillus sp. (n=1). The mean interval between implantation and removal was 14.0 ± 8.1 months. Following the initial implantation, antibiotics had been administered in all patients (Cefazolin, n=3). In the follow-up, there had been no occur infection nor wound healing impairment in these three patients.

Conclusion: Our data shows that biofilm formation with possibly pathogenic bacterial was occur on neurostimulation systems even in patients with well-healed wounds and despite administration of prophylactic antibiotics.

#186

Directional steering: clinical observations from an intraoperative study with a 32-contact lead

Maria Fiorella Contarino (1), Lo Bour (1), Rens Verhagen (1), Marcel Lourens (1), Rob de Bie (1), Pepijn van den Munckhof (2), Rick Schuurman (2)

1. Neurology, AMC, Amsterdam, Netherlands

2. Neurosurgery, AMC, Amsterdam, Netherlands

Objectives: 1) To confirm that stimulation through a new 32-contact lead is safe and can produce equivalent effects as stimulation through currently available DBS leads with 4 large annular contacts. 2) To establish whether stimulation with directional steering can modulate the thresholds of stimulation-induced clinical effects and side effects, thus providing the option to optimize the therapeutic window.

Methods: Eight patients with Parkinson's disease were included in the study. The new 32-contact lead was temporarily inserted during surgery. Double blind intraoperative test was performed to evaluate the threshold for benefit and the threshold for side effects in a "ring mode" and in 4 different randomized steering directions with the 32-contact lead (Sapiens Steering Brain Stimulation B.V., Eindhoven, The Netherlands), and in monopolar mode with the 3389 lead (Medtronic, Minneapolis, MN).

Results: There were no adverse events related to the experimental device. Sixteen out of 18 observed effects (88.9%) occurred at comparable threshold between the 32-contact lead in ring mode and the 3389 lead in monopolar mode. In 13 out of 15 side effects (87%) thresholds obtained with ring mode stimulation were different (≥ 1 mA) than those obtained in at least one steering direction.

Conclusion: Stimulation through the new 32-contact lead is safe and able to reproduce the clinical effects of the existing DBS leads. In addition it provides effective directional steering of the stimulation field, which can potentially improve the therapeutic window.

#189

Dynamic change of synchronized temporal patterns of somatosensory evoked potentials within thalamus following median nerve stimulation in Parkinson's disease and essential tremor patients

Katsushige Watanabe (1), Sumito Sato (2), Futaba Maki (3), Yasushi Okamura (4), Makoto Taniguchi (5), Fusako Yokochi (6)

1. Department of Neurosurgery, Tokyo Metropolitan Matsuzawa Hospital, Tokyo, Japan

2. Department of Neurosurgery, Kitasato University School of Medicine, Kanagawa, Japan

3. Department of Neurology, St. Marianna University School of Medicine, Kanagawa, Japan

4. Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital, Tokyo, Japan

5. Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan

6. Department of Neurology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan

Introduction: Event-related responses provide an exceptionally high temporal resolution tool for studying brain function and dysfunction, and reflecting the stages of information processing in the brain, while event-related frequency changes are considered an important indicator of the underlying brain processes, mechanisms and dynamics. In the classical point of view, the analysis of event-related brain dynamics is based on the assumption that the stimulus presentation evokes new strictly time-locked event-related neural activity which is superimposed on the background activity. An alternative view suggests that the presentation of the stimulus induces changes (phase resetting) of the background rhythmic dynamics only. The merits of each viewpoint have been subject to intense debate and scrutiny. The two hypotheses are usually assessed by means of statistics in the time-frequency domain such as some form of time-localized Fourier decomposition of single trials. Currently, however, intertribal phase correlation is taken as evidence for phase resetting at given frequency and latency. Previous studies demonstrated that thalamic oscillatory activities were commonly found and median nerve stimulation evoked potentials in the nucleus ventralis intermedialis (Vim) of the thalamus in Parkinson's disease and essential tremor patients. In fact, the Vim is believed to receive kinesthetic projections including muscle afferent projections. We therefore investigated the impact of median nerve stimulation on oscillations of neuronal populations in Vim and whether reorganization of background thalamic activity contributes to the generation of the evoked responses in thalamus.

Methods: We recorded median nerve stimulation-elicited somatosensory evoked potentials (SEPs) from the ventralis intermedialis (Vim) thalamus with semi-microelectrodes during stereotactic surgery in 7 patients with Parkinson's disease (n=3) and essential tremor (n=4). We here calculated the phase-locking factor (PLF) in order to measure the phase correlation of ongoing local field potentials (LFPs) oscillation across trials for given frequency bands in the generation of the SEPs in Vim thalamus.

Results: We found phase-locking of firstly γ and subsequently β frequency band of ongoing thalamic LFP oscillation at early period following the stimulation, and following phase-locking of θ and α band at late period across trials in about two thirds of evoked LFPs examined. Transition across trials from uniform to packed phase distribution revealed temporal phase reorganization of given rhythms of thalamic LFP oscillation in relation to stimulation. Otherwise, exclusive slower frequency oscillations such as θ and α band were observed at late period in some LFP responses, while no obvious higher frequency band appeared at early period.

Conclusion: The identification of a phase-locking in each rhythm of thalamic SEP trials reinforces the contribution of phase resetting model for global somatosensory information processing. Accordingly, a sound physiological comprehension of the stimulation induced dynamics of brain rhythms will probably contribute to an improvement of DBS techniques.

Brain oscillators are not independent, however. That is, the same neuronal assemblies or pools might be responsible for all rhythms. However, when the rhythm is fast, only small groups can follow the beat perfectly because of limitations of axon conductance and synaptic delays. Slower oscillations, spanning numerous axon conduction delay periods, on the other hand, allow the recruitment of very large numbers of neurons. Thus, the slower the oscillation such as θ and α band, the more neurons can participate; hence, the integrated mean field is larger than that of faster oscillation.

Understanding characteristic transient responses of neuronal populations to external stimulations may provide us with invaluable clues for investigating how the central nervous system such as thalamic nucleus reacts and adapts to the stimulus perturbations. For the therapeutic applications, however, it is a great challenge to design deep brain stimulation (DBS) techniques as effective as possible.

#196

Infected implantable devices. Treatment without removal.

Marios Themistocleous (1), Christos Anagnostopoulos (1), Aristotelis Kalyvas (1), Konstantinos Themistoklis (1), Stefanos Korfias (1), Damianos Sakas (1)

1. Neurosurgery Department, Evangelismos General Hospital, Athens, Greece

Submitter: Mr Anagnostopoulos Christos (GR)

Introduction: One of the rare but devastating complications of neuromodulation techniques is the implantable device infection. In the majority of the cases removal of the device is required, despite appropriate antibiotic therapy. We demonstrate that eradication of an implantable device infection is feasible without removal of the device.

Methods: Between 2002-2013, we implanted 531 neuromodulation devices in 450 patients. We report our experience in treating 13 patients; 7 patients suffering from infection of the internal pulse generator (IPG) who underwent deep brain stimulation for advanced Parkinson's Disease, 4 patients with infection of the intrathecally-delivering pump and 2 patients with infection of the spinal cord stimulator. Patients were treated with antibiotic therapy, surgical revision of the wound, intraoperative disinfection of the IPG and relocation of the subcutaneous pocket. In 11 cases (83%), the infection was eradicated and therapy was continued uninterrupted.

Results/conclusion: Although not generally recommended, neuromodulation devices may be salvaged in selected cases of superficial infection. Our experience suggests that it is possible to treat an infection without removing the device.

Our experience indicates that if the treatment is offered promptly, according to our protocol, it is possible to treat infection without removing the device. With this approach, the patients may be spared of therapy interruptions and additional procedures for the replacement of the device.

#204

Chronic spinal cord stimulation in medically intractable orthostatic tremor: longterm follow-up

Tamara Sauer (1), Christian Blahak (1), Goetz Luetjens (2), Assel Saryyeva (2), Hansjoerg Baezner (3), Hans-Holger Capelle (4), Michael Hennerici (1), Joachim K. Krauss (4)

1. Neurology, University School Mannheim, Mannheim, Germany

2. Neurosurgery, Medical School Hannover, Hanover, Germany

3. Neurology, Bürgerhospital, Stuttgart, Germany

4. Neurosurgery, Medical School Hannover, Hannover, Germany

Objective: To report the long-term follow-up results of spinal cord stimulation (SCS) in four patients with medically intractable orthostatic tremor (OT).

Introduction: OT is a rare form of tremor (13-18Hz) that occurs in the legs when standing upright. It is characterized clinically by increasing unsteadiness that disappears with walking or sitting down and often leads to significant disability due to the reduction of the ability to stand unsupported. Medical treatment frequently is unsatisfactory, thus in selected cases surgical treatment like SCS or thalamic deep brain stimulation have been proposed.

Methods: SCS was performed in four patients (mean age 67.5 \pm 5.9 years) with medically-intractable orthostatic tremor via 4- or 8-pole plate electrodes implanted at the lower thoracic spine and connected to programmable implantable pulse generators (IPG). Follow-up (FU) ranged between 34-133 months (mean 71 \pm 37 months). Outcome was assessed by recording the time tolerated to stand still pre- and several times postoperatively and by a simple patient self rating (PSR) scale (range 0 = poor to 6 = excellent). Furthermore, surface electromyogram (EMG) recordings of different leg muscles were performed to estimate tremor burst amplitude with and without SCS postoperatively.

Results: With chronic SCS, at last available FU (mean voltage 3.9 \pm 1.8V, frequency 130Hz and median pulse width 210 μ s in a range of 120-300 μ s) all four patients showed a subjective and objective improvement of unsteadiness occurring in the presence of stimulation-induced paraesthesia of the legs. The mean standing time improved from 51 \pm 47s pre-OP to 220 \pm 184s at last FU, the mean tremor burst amplitude in the EMG of tibialis anterior muscle was reduced by 30-60% with SCS compared to off SCS. PSR score was 4 or 5 in three patients and 3 in the other.

Conclusion: SCS can be an effective long-term treatment option in patients with otherwise intractable orthostatic tremor. In spite of the small sample size there is evidence for a negative correlation between the preoperative OT severity and the therapeutic effect of SCS.

#213

Altered taste during thalamic DBS stimulation can be normalized with interleaved stimulation

Anna-LEna Törnqvist Jensen (1), Natalie Montevert (2), Hjalmar Bjartmarz (2)

1. Department of Neurosurgery, Skåne University Hospital, Lund, Lund, Sweden

2. Department of Neurosurgery, Skåne University Hospital, Lund, Lund, Sweden

Objective: Determine if the patients regained “normal” taste in mouth with interleaved DBS stimulation while preserving the tremor reduction with DBS.

Introduction: Seven out of our > 200 patients with thalamic DBS have reported change of taste in the mouth with DBS on or an explosion of metallic taste when turning DBS off or on. Two case reports have been presented on agusia during VIM DBS treatment. One suggested explanation is that the spread of the electrical field reach the ventro posteromedial thalamic nuclei (VPM) or its fibre tracts.

Methods: The three essential tremor patients at our department who perceived a persistent change of taste in mouth during bilateral VIM DBS treatment reducing the tremor with at least 75% were included. The four patients who only perceived metallic taste when turning DBS off or on were excluded. The electrical fields was focused around the most effective contacts for reducing tremor while attempting to avoid spread to VPM or fibres thereof. This was done by using two electrical programs/lead while also taking the overlapping electrical fields/lead into account, regarding the overlapping electrical field as a third field. Perception of taste was described by the patients and tremor was assessed during drinking and eating activities.

Results: In two of three patients the taste in mouth were perceived as normal and they had unchanged or better tremor reduction with stimulation as compared to before changing this. However, one patient did still perceive a change of taste but now for the better, he had sweet taste instead of bitter. The new settings with placement of the electrical fields along the lead were similar to the ones giving altered taste, but had another shape.

Conclusion: Interleaved stimulation may be a possible solution to overcome side effects of the electrical field causing change in taste in patients with thalamic DBS while keeping or improving the tremor reduction. This strategy can be an option for avoiding other unwanted effects of the electrical field in patients treated with DBS.

#268

Should lead Penetration of the Caudate Nucleus be avoided in DBS surgery for Parkinson's Disease?

M. Bot¹, MD, R.M.A. de Bie², MD PhD, P. van den Munckhof, MD¹ PhD, P.R. Schuurman¹, MD PhD

Dept of Neurosurgery¹ Academic Medical Center, Amsterdam, NL; Dept of Neurology² Academic Medical Center, Amsterdam, NL;

Introduction: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is associated with a mild postoperative cognitive decline in a proportion of Parkinson's Disease (PD) patients. Recent literature suggests that lead penetration of the Caudate Nucleus (CN) could negatively influence neurocognitive outcome and should therefore be avoided. This subcortical nucleus is well delineated on preoperative magnetic resonance imaging (MRI) so that avoidance would be feasible to implement. We aim to determine the influence of lead trajectories traversing the CN on neurocognitive outcome in DBS surgery for PD.

Methods: Lead trajectories in PD patients that underwent STN deep brain stimulation between 2001 and 2006, when the CN was not yet systematically avoided, were evaluated on postoperative computed tomography (CT) fused with preoperative stereotactic 1.5-Tesla T1 MRI. Trajectories were determined to be inside, outside or in border region of the CN. The trajectory groups were subsequently compared with pre- and postoperative neurocognitive tests in order to detect difference in patients cognitive functioning. Detailed neuropsychological assessments were available at baseline and 12 months after surgery.

Results: 106 electrode tracks in 53 patients were evaluated. Bilateral penetration of the CN occurred in 8 (15.1%) and unilateral in 16 (30.2%) patients. In 19 (35.9%) patients tracks were located in the border region of the CN. There was no electrode penetration of the CN in 10 (18.9%) patients. No difference in neurocognitive outcome was found between the different groups.

Conclusion: Neurocognitive outcome was not influenced by DBS electrode tracks traversing the CN. It seems both feasible and sensible to avoid electrode tracks through the CN when possible. However, penetration of the CN could be considered when this facilitates more optimal trajectory planning.

1.2.2 Psychiatric Disorders

#43

LONG TERM RESULTS OF POSTEROMEDIAL HYPOTHALAMIC DEEP BRAIN STIMULATION FOR PATIENTS WITH RESISTANT ERETHISM

Cristina Torres (1), Rafael Sola (1), Jesus Pastor (2), Elena Ezquiaga (3), Eduardo García-Camba (3)

1. Neurosurgery, Hospital La Princesa, Madrid, Spain

2. Clinical Neurophysiology, Hospital La Princesa, Madrid, Spain

3. Psychiatry, Hospital La Princesa, Madrid, Spain

Introduction: Erethism defines severe cases of aggressiveness associated with mental retardation, usually in relation to perinatal brain damage. When this aggressiveness is resistant to pharmacological therapy, seriously impairs the affected individual's ability to interact, causing a significant individual, social and economical impact.

Deep brain stimulation (DBS) at the posteromedial hypothalamus (PHN) has been proposed as a treatment for resistant erethism, although experience around the world is very scarce. The objective of this study is to examine the long term outcomes of DBS at the PHN, in 7 patients with severe erethism treated in our institution.

Methods: Medical records of 7 patients treated with DBS at the PHN, for intractable aggressiveness, were reviewed. The therapeutic effect on behaviour was assessed by the "Inventory for client and agency planning (ICAP)", at baseline, and at the last follow-up.

Results: Two patients died due to causes unrelated to the neurosurgical treatment. Five out to seven patients experienced a significant reduction in aggressiveness (mean general aggressiveness ICAP score was -47 at baseline, and -25 at the last follow-up, mean 60 months). Similar response was obtained with low and high frequency stimulation. Four patients' sleep pattern became more regular, and one patient stopped previous binge eating and potomania. One out to three epileptic patients noticed a 30% seizure frequency reduction. None experienced relevant side effects.

Conclusion: DBS at the PHN successfully treated refractory erethism in our series. Prospective controlled studies with a larger number of patients are needed to confirm these results.

#73

Is the proper DBS target for OCD patient-specific?. Multimodal fMRI-DWI to predict success of striatal DBS in obsessive compulsive disorder

Juan A. Barcia (1), Jose Angel Pineda-Pardo (2), Josue Avecillas-Chasin (1), Rocio Arza (3), Bryan Strange (4)

1. Neurosurgery, Hospital clinico San Carlos, Madrid, Spain

2. Neuroscience, Laboratory for Clinical Neuroscience Centre for Biomedical Technology, Madrid, Spain

3. Psychiatry, Hospital clinico San Carlos, Madrid, Spain

4. Clinical Neuroscience, Laboratory for Clinical Neuroscience Centre for Biomedical Technology, Madrid, Spain

Introduction: In patients with obsessive compulsive disorder (OCD), the efficacy of DBS remains variable. We explored whether efficacy of DBS in OCD may depend on the locus of stimulation within striatum in a patient-specific manner.

Methods: 4 patients with OCD were included in the study with 2 years of follow-up. To acquire fMRI data, we employed a modified version of the OCD symptom provocation paradigm using the Maudsley Obsessive–Compulsive Stimuli Set (MOCSS). The study comprised 4 'blocks', where patients were presented with pictures of 4 classes of provocative stimuli: washing, checking, hoarding, symmetry and neutral. Each block consisted of ten 20s alternating epochs in which subjects viewed either 10 provocative or 10 neutral pictures. We specified four effects of interest: the epochs corresponding to each symptom dimension. Events corresponding to viewing instructions, and questions regarding anxiety levels, were modeled as separate regressors. Six movement parameters were modelled as nuisance covariates. During surgery, a trajectory was planned to reach the target at the NAc, and to place the contacts at several points along the striatum. Anatomical connectivity (AC) was quantified using probabilistic tractography, and fMRI prefrontal activations were used as seeds. We identified clusters of AC coming from the seed ROIs to the striatum, and computed the distance of the deep electrodes to the clusters.

Results: The electrodes that provided the best outcomes were 1st for patient 1, 2nd for patient 2 and 4th for patient 3. We observed some dependence between the AC clusters location in striatum and the electrodes that caused some improvements in patients 2 and 3 and also for patient 1, where the second highest AC peaks were close to the best electrode.

Conclusion: Our preliminary data suggest that the combination of symptom provocation fMRI and probabilistic tractography may provide a basis for tailoring the target of electrode implantation on a patient specific basis.

#114

Long-term results of posteromedial hypothalamic deep brain stimulation in resistant epilepsy associated to aggressive behavior.

Juan Carlos Benedetti-Isaac (1), Martin Torres-Zambrano (2), William Omar Contreras Lopez (3), Randy Guerra-Olivares (4), Esther Perea-Castro (5), Gabriel Alcala (6), Thomas Reithmeier (7), Luciano Furlanetti (8)

1. Functional Neurosurgery, Latin American Research Epilepsy Center, CLIE, Cartagena, Colombia

2. Neurology, Colombian Foundation Center for Epilepsy and Neurological Diseases, FIRE, Cartagena, Colombia

3. Functional and Stereotactic Department, University of Sao Paulo, Sao Paulo, Brazil

4. Functional Neurosurgery, Latin American Research Epilepsy Center, CLIE, Cartagena, Colombia

5. Neurology, Latin American Research Epilepsy Center, CLIE, Cartagena, Colombia

6. Functional Neurosurgery, Colombian Foundation Center for Epilepsy and Neurological Diseases, FIRE, Cartagena, Colombia

7. Neurosurgery, Munchen University, Freiburg, Germany

8. Functional and Stereotactic Neurosurgery, Freiburg University Clinic, Freiburg, Germany

Introduction: Deep brain stimulation (DBS) of the posteromedial hypothalamus (PMH) has been proposed as a treatment for untreatable aggressiveness. Aggressive behavior may be related to organic brain damage, concomitant psychiatric disorders, intellectual disability and epilepsy. In our center we realized that some patients who received PMH DBS interestingly diminished seizure frequency postoperative. Base on that previous experience, the objective of this study was to examine the outcome of PMH DBS in reduction in seizure frequency in patients with aggressiveness and associated drug-resistant epilepsy (DRE).

Methods: Seven patients with intractable aggressive behavior underwent bilateral stereotactic pHyp-DBS. Out of these three patients presented concomitant DRE. Medical records were reviewed. Postoperative therapeutic effect on behavior was measured using the modified overt aggression scale (MOAS). Epilepsy outcome was assessed by reduction of seizures frequency and antiepileptic medication at 18 month follow-up.

Results: All seven patients experienced a significant reduction in aggressiveness (from an average of 18 to 7.5 points) in MOAS . The three patients with previous history of epilepsy followed a significant improvement in the Engel outcome scale, achieving 88.6% reduction of the seizure frequency.

Conclusion: In well-selected patients, DBS of the PMH seems to be an effective treatment strategy for DRE associated with aggressive behavior. Larger and prospective series are needed; however we certainly proposed to include the PMH as a valid experimental target for DRE.

#134

A model for modernity? Interpreting outcome data for the stereotactic subcaudate tractotomy (SST).

Christine Matthews (1), Keith Matthews (1)

1. Division of Neuroscience, University of Dundee, Dundee, United Kingdom

Introduction: Devised by the neurosurgeon Geoffrey Knight, the stereotactic subcaudate tractotomy was a modification of the orbital undercut. By 1976, SST was the most frequently performed surgical intervention for the treatment of mental illness in the UK. A significant body of literature describes the lesion and promising clinical outcomes were reported. However, there was debate about the efficacy of SST as compared with other surgical approaches. Although the use of some related procedures continued, until recently SST was largely of historical interest. Today, neural structures affected by the SST lesion are being investigated as potential targets for deep brain stimulation (DBS) technologies. Currently, no dedicated, independent review of SST outcomes exists. Systematic reviews, such as Andrade et al (2010), assess a variety of neurosurgical interventions. Therefore, they are unable to provide a fully comprehensive interrogation of the available records. Issues associated with changes in technique, the unreliability of pre-operative diagnoses (modern instruments and syndrome specific rating scales were not available) and the conflation of different diagnoses within outcome data continue to make interpretation difficult. Importantly, significant repeat reporting exacerbates this.

Methods: To address this, we conducted a systematic search for records dating from 1960. The search terms "SCT", "SST", "subcaudate", "tractotomy", "limbic leucotomy", "innominat*" and "yttrium" were employed. This was not restricted to English language; however we did not employ search terms for other languages. We also followed references in printed material to identify information which was not captured by the digital search. After initial screening at title and abstract level, papers reporting the use of SST for the treatment of psychiatric illness were retrieved and examined. Those providing outcome data and wider contextual information were retained. Context was used to establish a framework within which outcome studies were located. By removing potentially overlapping papers, an estimate of numbers could be made. This allowed a conservative assessment of outcomes. For the purposes of this review, a categorical GOOD outcome was defined according to the Global Outcome Scale (Pippard, 1955).

As a relatively small number of evaluable cases originated outside the UK, these papers are not considered here.

Results: Of 7337 papers retrieved, 515 (7%) were relevant to the topic. Duplicates were removed and after examination at abstract level, 94 papers were retained for full examination. Relevant outcome information was available in only 52 (10%) papers.

A total of 1300 SCT operations performed at the Geoffrey Knight Unit (GKU) in London were described in 12 papers. There was no overlap in reporting for 3 papers describing 704 (54%) of GKU cases. In 252 cases, outcome data was extracted in a case note review. For these patients, 84 (33%) had a GOOD outcome following surgery. A further 284 patients were fully assessed at follow up by external review. Of these, 151 (53%) had a GOOD outcome after SST. This equates to 12% of the total population treated at the Geoffrey Knight Unit. Pre and postoperative assessment is available for only 23 (2%) patients.

Conclusion: Over 1300 stereotactic subcaudate tractotomy (SST) operations were conducted at the GKU in London between 1960 and 1995. However, only a proportion of these patients are reported in the literature. An even smaller number were assessed by independent review - with pre and postoperative data available in only 2% of cases. Therefore, it may be wise to exercise caution when interpreting the SST literature. This review supports the call for improved and consistent standards of reporting, with inclusion of all patients in case series reports and the avoidance of duplication in publications reporting the outcomes of neurosurgical interventions for the treatment of mental illness (Nuttin et al, 2014).

#152

Morbid obesity treated with bilateral nucleus accumbens stimulation – a two cases report

Marek Harat (1), Marcin Rudaś (1), Paweł Sokal (1), Piotr Zieliński (1)
1. Neurosurgery, Military Research Hospital, Bydgoszcz, Poland

Introduction: We present two cases of patients with morbid obesity, treated by bilateral deep brain stimulation of the nucleus accumbens. In both cases, the starting point of illness was the operation of the craniopharyngioma with multihormonal hypothalamic pituitary deficiency.

Methods: We treated two obese, female patients M. K. (BMI = 52.64, weight = 150.7 kg) and N.Z. (BMI = 46.77, weight = 132kg) with bilateral nucleus accumbens (NACC) stimulation. Surgeries were performed in the Department of Neurosurgery in Military Research Hospital in Bydgoszcz, Poland in years 2012 and 2014. Patients gave the informed consent on surgical treatment defining risks, potential benefits according to the recommendations of the Medical Ethical Committee.

Results: After a month body weight of the first patient M. K. was lower from baseline more than 7kg, after 1 year of follow-up the reduction of weight was 20kg. We did not observe any complications and side effects during the period of stimulation. The neuropsychological study showed no deviation from the norm, especially without cognitive impairment. The patient feels well, thinking about food intake about 20% of the daily activity, before surgery it was 80%. In the course of treatment the stimulation has been interrupted twice - the first time because of the stimulator was turned off, the second time because of breakage of connecting cables. In both situations, the patient reported strong deterioration of symptoms. At present the patient conducts normal life as a student of the university. The second patient N.Z. feels well, can control food intake, does not have to eat during the night (before surgery - every 2 h). Time devoted for thinking about eating was reduced from 90% to 50% during the day. During the day the quantity and quality of meals does not deviate from the norm, the patient no longer feels compulsion to food intake.

Conclusion: In our opinion, based on preliminary results in patients described above, nucleus accumbens stimulation seems to be effective and safe procedure in morbid obesity.

#171

GK radiosurgery in intractable psychiatric disorders

Jung Kyo Lee (1), Seung Yoon Kim (2), Tae Kyung Lee (3), Eun Ki Chung (3)

1. Neurosurgery, Asan Medical Center, Seoul, South Korea

2. Psychiatry, Asan Medical Center, University of Ulsan, Seoul, South Korea

3. Psychiatry, Seoul National Hospital, Seoul, South Korea

Introduction: There is current interest in the use of surgical management in intractable psychiatric disorders. Recently, 140-160 Gy of gamma knife radiosurgery for intractable OCD disorders was effective and safe in literature.

Methods: We have treated 5 patients with GK radio surgery (3 patients -OCD, 1patient - MDD, 1 patient - impulse control disorder), who were followed for longer than 6 months since 2012.12.

All patients were medically intractable and recurrent even ECT. Gamma capsulotomy with 140 Gy in OCD, gamma subcaudate tractotomy with 130 Gy in MDD and gamma cingulotomy with 160Gy in impulse control disorder were performed with improvement.

Results: Marked improvement was noted at 4 months after gamma knife radio surgery from 23 to 4 in Hamilton rating scale for depression and from 6 to 3 in clinical global impression for MDD patient. The radiosurgical brain edema was noted in a patient who were treated with 160Gy, however it was completely resolved with steroid management.

Conclusion: Gamma knife radiosurgery could be the surgical option for patients in intractable psychiatric disorders

#180

Rechargeable neurostimulators in deep brain stimulation for obsessive-compulsive disorder: experience in a series of 10 patients.

Philippe De Vloo (1), Simon Raymaekers (2), John Das (3), Loes Gabriëls (2), Bart Nuttin (4)

1. Laboratory for Experimental Functional Neurosurgery, KU Leuven, Leuven, Belgium

2. Department of Psychiatry, University Hospitals Leuven, Leuven, Belgium

3. Research group Experimental Neurosurgery and Neuroanatomy, KU Leuven, Leuven, Belgium

4. Department of Neurosurgery, University Hospitals Leuven, 3000, Belgium

Introduction: From 1999 onwards, Deep Brain Stimulation [DBS] has been proposed as an alternative to capsulotomy in refractory cases of OCD. Although rechargeable implanted pulse generators [rIPG] in DBS for OCD patients have been used in at least two described cases, there are no reports on the efficacy, applicability, safety and the diminishment of the need of IPG replacement in this highly specific population. Authors have called for prudence on the use of rIPGs in DBS for OCD. One could fear obsessions and compulsions regarding battery recharging and checking. Further, a depressive mood could interfere with the strict recharging needs that come with an rIPG, while IPG depletion has the potential to lead to emergence of depression, anxiety, and suicidality.

The aim of this study is to share our experience in DBS for OCD patients that have been implanted with an rIPG after end-of-life of at least their second non-rechargeable IPG.

Methods: In October 2007, a prospective study was set up, in which OCD patients needing frequent IPG replacements (more than once per two years) were proposed to receive an rIPG at the next IPG replacement. Ten patients were analysed in this study.

Results: Five male and five female OCD patients with a mean age of 44 years (range 28y5m-63y7m) that were on average 5 years and 11 months (range 2y5m-9y2m) treated with DBS underwent implantation of a n rIPG. They all needed frequent battery changes while using non-rechargeable IPGs (mean longevity of last depleted IPG 243 days). Yale-Brown Obsessive Compulsive Scale [Y-BOCS], Hamilton Rating Scale for Depression, Global Assessment of Functioning, Hamilton Anxiety Rating Scale and Beck Depression Inventory were recorded at least one time per six months during the 2 years before and the 2 years after implantation of the rIPG. No significant differences were noted for all five scores during the two years before as compared to the two years after rIPG implantation. Y-BOCS was 14.24 ± 4.40 SEM and 14.45 ± 3.98 SEM in the two years before and after rIPG implantation, respectively. No significant changes in programmed stimulation parameters nor medication use were noted in the 2 years after as compared to the 2 years before rIPG implantation. The frequency of DBS-related surgical procedures dropped dramatically after rIPG implantation as compared to before implantation (1.39 vs. 0.05 per follow-up year, respectively). Recharging parameters, as displayed by the physician's programming device, showed a mean recharging frequency of 2.2 times per day and 1.4 times per day within the first six months and within the following 18 months, respectively. When asked for it, no patient mentioned compulsive recharging behavior, though one patient mentioned the need to recharge to 100% loading status at each recharging session. There were no infections during the period between first DBS electrode implantation and the end of follow-up. Only one patient experienced major recharger antenna-rIPG coupling problems. He had experienced extreme weight loss in the first six months following bariatric surgery. The skin overlying the rIPG had become very abundant and loose, making it hard to obtain a stable position of the recharger antenna in relation to the rIPG. One patient experienced a battery depletion associated with a very sudden OCD-related symptom worsening, though she had recharged regularly in the days before. It turned out that the recharger had broken down. After replacement of the recharger, the problem did not re-occur. The recharger's belt broke at least once in 6 of our 10 patients.

Conclusion: We publish the first series on rIPGs in DBS for OCD patients. Based on this preliminary experience, we believe that the use of rIPGs in this specific population is effective in keeping the psychiatric assessment scores at the same level as while using non-rechargeable IPGs, without raising the stimulation amplitude nor the need for psychiatric drugs.

From our observations, we believe that the use of rIPGs is applicable in these patients, with all of our patients capable to recharge without patient attributed battery depletions. Moreover, it seems to be a safe technique, which decreases the frequency of IPG replacements.

Based on these results, approval and reimbursement of the use of rIPGs for DBS in OCD seems justified.

#194

Event-related potentials in the bed nucleus of the stria terminalis/ internal capsule in response to neutral and aversive stimuli in OCD

Mesbah Alam (1), Lotta Winter (2), Kerstin Schwabe (1), Hans H. Heissler (1), Lütjens Goetz (1), Kai Kahl (2), Joachim K Krauss (1)

1. Department of Neurosurgery, Hannover Medical School, Hannover, Germany

2. Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany

Introduction: The present study aims to characterize the evoked related potentials (ERPs) measured during natural and aversive visual stimuli in the bed nucleus of the stria terminalis/ internal capsule (BNST/IC) in patient with obsessive-compulsive disorder (OCD), and the effects of metacognitive therapy (MCT) thereof. MCT belongs to the most recent developments in cognitive behavioural therapy. Deep brain stimulation (DBS) is an innovative therapy for patients with treatment-refractory OCD (trOCD), aiming at the normalisation of abnormal activity in cortico-striato-thalamo-cortical circuits. Postoperative recording via externalized leads of the stimulation electrodes allows for assessment of intracranial neuronal activity.

Methods: Evoked related potentials (ERPs) were directly recorded via electrodes implanted for DBS in the BNST in one patient with trOCD while viewing neutral and aversive pictures. Thereafter, intensive MCT was applied for four days. Finally, neutral and aversive pictures were shown and assessment of ERPs was done as described before with using the latency of P300 as measure.

Results: Before therapy the latency of P300 was reduced after aversive stimuli as compared to neutral stimuli ($p < 0.05$), while after MCT, the latency was enhanced ($p < 0.05$).

Conclusion: We show that the neuronal response of BNST differs between neutral and aversive pictures in OCD, and that MCT has an impact on this neuronal response. These results suggest that the BNST/IC is involved in sensory and cognitive information processing in OCD.

#202

Nucleus accumbens deep brain stimulation as treatment option for binge eating disorder?

R Lok (1), M Verhagen (2), L Staal (1), J Van Dijk (2), A van Beek (3), Y Temel (4), A Jahanshahi (4), M Staal (2), G van Dijk (1)

1. Neuroendocrinology, University of Groningen, Groningen, Netherlands

2. Neurosurgery, University Medical Center Groningen, Groningen, Netherlands

3. Endocrinology, University Medical Center Groningen, Groningen, Netherlands

4. Neuroscience, Maastricht university, Maastricht, Netherlands

Introduction: Binge eating disorder (BED) has been postulated to arise from mesolimbic dopaminergic system changes, presumably homologous to those seen in drug addiction. Deep Brain Stimulation (DBS) is regarded as a relatively novel but promising surgical treatment of addiction. Because of potentially similar circuitries underlying drug addiction and BED, we aimed to investigate Nucleus Accumbens DBS as treatment option for BED.

Methods: Wistar-rats had electrodes placed in the Nucleus Accumbens core (NAcc core) or lateral shell (NAcc lShell) or medial shell (NAcc mShell) and were adapted for several weeks to high fat food (HFF) binge eating protocol, with one-hour food deprivation preceding a one hour access to HFF (binge) at the penultimate hour before the dark phase. DBS was applied either before and/or during the binge and was varied in stimulation currents and frequencies.

Results: With respect to the NAcc core, the most striking results were achieved when stimulating with a current of 250 μ A before binge at 10Hz (intake = 61%, $p=0.0076$), while no effects were found when stimulation was performed during the binge. DBS in the NAcc lShell showed strongest suppression of the binge when stimulating with either 125 or 250 μ A during binge at 50Hz (intake =56%, $p=0.00331$), but no effects were observed when stimulation was performed before the binge. No significant results were achieved when stimulating NAcc mShell.

Conclusion: These data indicate that DBS of the NAcc core suppresses the “wanting” aspects of bingeing whereas DBS of the NAcc lShell suppresses “liking” aspects of bingeing. “Wanting” changes the food reward potency, and these aspects have indeed been found to reside in the NAcc core. Furthermore, incentive hotspots associated with “liking” have previously been identified in lateral parts of the NA. We conclude that DBS in the NAcc may be a promising tool for the treatment of BED in human patients.

1.2.3 Epilepsy

#12

Improved localization of implanted subdural electrode contacts on MRI using an elastic image fusion algorithm in invasive EEG recording

Lennart Stieglitz (1), Christian Ayer (2), Markus Oertel (2), Roland Wiest (3), Claudio Pollo (2)

1. Neurosurgery, Zurich University Hospital, Zurich, Switzerland

2. Neurosurgery, Inselspital Bern, Bern, Switzerland

3. Neuroradiology, Inselspital Bern, Bern, Switzerland

Introduction: Accurate projection of implanted subdural electrode contacts in the invasive recording phase in pharmacoresistant epilepsy cases is highly relevant. Rigid fusion of CT and MRI may display the contacts in the wrong position due to brain shift effects.

Methods: To evaluate the ability of an elastic image fusion algorithm to provide a more accurate projection of the electrode contacts on the pre-implantation MRI we performed a retrospective study in five patients. An automated elastic image fusion algorithm (AEF), a guided elastic image fusion algorithm (GEF) and a standard rigid fusion algorithm (RF) were used on preoperative MRI and post-implantation CT scans. Vertical correction of virtual contact positions, total virtual contact shift, correction of midline shift and brain shift due to pneumocephalus were measured.

Results: Both AEF and GEF worked well with all 5 cases. An average midline shift of 1.7mm (SD 1.25) was corrected to 0.4 mm (SD .8) after AEF and to 0mm (SD 0) after GEF. Median virtual distances between contacts and cortical surface were significantly corrected from 2.3mm after RF to 0mm after AEF and GEF ($p < .001$). A mean total relative correction of 3.11mm (SD 1.85) after AEF and 3.0mm (SD 1.77) after GEF was achieved. The tested version of GEF did not achieve a satisfying virtual correction of pneumocephalus.

Conclusion: The technique provides a clear improvement in fusion of pre- and post-implantation scans, though the accuracy is difficult to evaluate.

#14

Deep Brain Stimulation of the nucleus accumbens – 1st experience in pharmacoresistant focal epilepsies

Friedhelm Schmitt (1), Alexander Kowski (2), Lars Buentjen (3), Patricia Panther (3), Julia Matzen (1), Wenjie Li (1), Hans-Jochen Heinze (1), Tino Zaehle (1), Martin Holtkamp (4), Frank Oltmanns (5), Juergen Voges (3)

1. Department of Neurology, University Magdeburg, Magdeburg, Germany

2. Department of Neurology, Charité – Universitätsmedizin Berlin, Germany, Berlin, Germany

3. Department of Stereotactic Neurosurgery, University Magdeburg, Magdeburg, Germany

4. Department of Neurology, Epilepsy-Center Berlin-Brandenburg and Charité – Universitätsmedizin Berlin, Germany, Berlin, Germany

5. Department of Epileptology, Epilepsy-Center Berlin-Brandenburg, Berlin, Germany

Introduction: Deep brain stimulation has developed to established treatment modality for difficult-to-treat pharmacoresistant epilepsies. However stimulation of the anterior thalamus is associated with increased complaints of memory impairment and depression. First results are presented, which assess efficacy and safety of chronic electrical stimulation of the nucleus accumbens (NAC) – a putative new target for patients with pharmacoresistant focal epilepsy.

Methods: Following a 3-month baseline period, all subjects (5 patients) underwent bilateral NAC stimulation for 6 months. Antiepileptic drugs remained unchanged throughout the study. Outcomes of interest were changes in median frequency of disabling seizures (sum of complex partial and generalized tonic clonic seizures) and proportion of responders ($\geq 50\%$ reduction of seizure frequency), also patient outcome questionnaires (Liverpool Seizure Severity Scale [LSSS], Quality of Life in Epilepsy questionnaire [QOLIE-31-P] and Beck Depression Inventory [BDI-IA]), psychiatric assessment by Mini International Neuropsychiatric Interview (M.I.N.I.) and extensive neuropsychological testing were assessed prior to electrode implantation and after 6 months of NAC stimulation.

Results: Two out of five participants were responders. The median reduction in frequency of disabling seizures was 37.5%. NAC stimulation resulted in significant decrease in seizure severity as assessed with LSSS ($p = 0.043$). QOLIE-31-P total score trended towards improvement ($p = 0.068$), whereas BDI IA-scores, M.I.N.I. and neuropsychological test scores remained unchanged.

Conclusion: In patients with pharmacoresistant focal epilepsy, chronic electrical stimulation of the NAC may be effective as indicated by median reduction in seizure frequency and decreased seizure severity. NAC stimulation leaves neurocognitive function and psychiatric comorbidity unchanged.

#15

Radiofrequency lesioning for focal epilepsies – a rational approach

Friedhelm Schmitt (1), Lars Buentjen (2), Johannes Klein (3), Joerg Wellmer (4), Christian Bien (5), Friedrich Woermann (5), Tilman Polster (5), Heinz Pannek (5), Reinhard Schulz (5), Hans-Jochen Heinze (1), Klaus Kopitzki (1), Juergen Voges (2)

1. Department of Neurology, University Magdeburg, Magdeburg, Germany

2. Department of Stereotactic Neurosurgery, University Magdeburg, Magdeburg, Germany

3. Department of Stereotactic Neurosurgery and Department of Neurosurgery, University Magdeburg and University Hospital Carl-Gustav-Carus, Magdeburg and Dresden, Germany

4. Department of Neurology, Ruhr-Epileptology, University Hospital Knappschaftskrankenhaus, Bochum, Germany

5. Mara Hospital, Epilepsy Center Bielefeld, Bielefeld, Germany

Introduction: With the increasing knowledge about seizure propagation - derived from experience in resective epilepsy surgery - stereotactic radiofrequency ablation (sRA) has lately been reconsidered as a minimal-invasive surgical option for focal epilepsies (Catenoix et al, Neurology, 2008 & Liscak et al, Acta Neurochir 2010). First results concerning efficacy and safety in four patients treated with sRA are presented.

Methods: All patients (2 females; median age 43.2 years [range 9.9 to 56.5 years]) were multiple pharmacoresistant (median 5 antiepileptic drugs [range 2 to 18]). The first seizures started with a mean of 29.7 years (range 6.9 to 53.5 years) prior to sRA. In all patients resective operative surgery was abandoned considering the results of standard presurgical evaluation. Two patients (both with a single left frontal periventricular nodular heterotopia [PNH]) received preoperative intracerebral video-eeg-monitoring and the remaining two patients (focal cortical dysplasia [FCD] Type IIb either in the left orbito-frontal or in the right pre-central gyrus) intra-operative EEG-recordings, respectively. The trajectories for sRA were planned using computed tomography (CT)/MRI-guided and computer-assisted treatment planning software (Voges et al, J Neurosurg 2002). The single coagulations were considered as virtual radioactive sources, defining the number of trajectories and treatment points necessary to fully cover the pre-operatively defined target volumes for the individual patient.

Results: Last follow up period was after 2.3 years (range 0.5 to 4.1 years). Three out of four patients obtained Engel Class I outcome (two with complete seizure freedom, one patient had rare non-disabling auras) and one patient had a significant seizure reduction (Engel Class IIIa). One patient (right pre-central FCD type IIb) had peri-operative complication (transient mild hemiparesis without functional deficit at follow-up of 1.2 years). Both patients, who did not achieve complete seizure freedom, had with a single PNH, which were not completely removed for safety reasons.

Conclusion: Provided the patients are carefully selected sRA is a safe and effective procedure both for epilepsies due to FCD or PNH. In this small cohort all patients with a FCD became completely seizure free, indicating entire removal of the epileptogenic zone. Whether this observation is due to the intra-operative EEG recordings, which only patients with FCD received, the pathology itself or the uncomplete removal of the PNHs will be discussed under consideration of the literature.

#155

Anterior nucleus of the thalamus (ANT) stimulation in epilepsy: stereotactic targeting and localization of effective contacts

Johannes A Koeppen (1), Berthold Voges (2), Patrick M. House (2), Fahimeh Nahravani (1), Torge Huckhagel (1), Andreas K Engel (3), Manfred Westphal (4), Stefan RG Stodieck (2), Christiane Kuhlmann (5), Alessandro Gulberti (3), Christian KE Moll (3), Wolfgang Ham

1. Klinik für Neurochirurgie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

2. Epilepsiezentrum Hamburg, Ev. Krankenhaus Alsterdorf, Hamburg, Germany

3. Institut für Neurophysiologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

4. Klinik für Neurochirurgie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

5. Neuromodulation, Medtronic, Inc, Meerbusch, Germany

Introduction: Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) has been approved for the treatment of selected patients suffering from epilepsy refractory to medical therapy. Both the surgical approach and the optimal site for stimulation are controversial.

Methods: In 13 patients (9 female; median age 34) an extraventricular approach was used for bilateral electrode implantation in general anaesthesia. The junction of the mamillothalamic tract with the ANT was targeted. Implantation of the permanent electrode was preceded by microelectrode recordings from a single trajectory. The stereotactic position of active contacts was derived from intraoperative computed tomography and analyzed by two different applications. First, a propriatory software tool served to determine the position of different electrode contacts with regard to the ANT as delineated in the Mai atlas. Second, an open source-based stereotactic software tool was developed to analyze the position of different electrode contacts with respect to the mammillothalamic tract and thalamus. To this end, both structures had been individually segmented from preoperative MRI using a free application (ITKSnap).

Results: For 11 patients, mean and median follow-up was 20 months. Two patients were excluded from this analysis, since their follow-up period was shorter than 6 months. A significant reduction of seizures was observed in 9 patients. Partial seizures were reduced by >75% in five patients and from 50 to 75% in four patients. Secondary generalization, if present, was reduced to at least the same extent. Furthermore, seizure duration and severity were also reduced. Two patients were rated as non-responders (seizure reduction <30%). Surgery-related complications, such as intracranial hemorrhages or infections, were not observed. Intraoperative microelectrode recordings revealed a typical pattern consisting of abundant bursting activity upon entering the thalamus which was followed by a silent segment of approximately 2 mm and the recurrence of sparse neuronal activity. The silent region was supposed to represent the transition from the thalamus to fiber structures, i.e. the mammillothalamic tract and/or the internal medullary lamina. Segmentation of the course of the mammillothalamic tract and the boundaries of the thalamus from preoperative MRI revealed a significant degree of individual as well as interhemispheric variation. Permanent stimulation was commenced and continued with contacts located in proximity to or within the mammillothalamic tract, and several of these contacts had been placed below the ANT proper. Since seizure suppression elicited by individual contacts or stimulation settings had to be assessed over months in order to draw reliable conclusions, a systematic evaluation of each contact with different settings is impracticable in epilepsy. However, the efficacy of the chosen contacts was corroborated by the fact that in several patients the stimulation amplitude could be lowered over time resulting in even improved seizure suppression.

Conclusion: 'ANT stimulation' performed by targeting of the upper end of the mammillothalamic tract using an extraventricular trajectory is a safe and effective approach. Based on 3D analysis of the anatomy of individual patients and respective electrode positions effective stimulation does not require placement of active contacts within the ANT proper. As for well-established DBS targets in movement disorder surgery fiber tracts are likely to mediate therapeutic effects.

#203

Seizure and neuropsychological outcome after stereotactic amygdalohippocampectomy for mesial temporal lobe epilepsy

Roman Liscak (1), Zdenek Vojtech (2), Hana Malikova (3), Lenka Kramska (2), Tomas Prochazka (2)

1. Stereotactic and radiation neurosurgery, Na Homolce Hospital, Prague, CzechRepublic

2. Neurology, Na Homolce Hospital, Prague, CzechRepublic

3. Radiodiagnostic department, Na Homolce Hospital, Prague, CzechRepublic

Introduction: The aim of the study was to evaluate the seizure and neuropsychological outcome and complications after stereotactic radiofrequency amygdalohippocampectomy (SAHE) performed for mesial temporal lobe epilepsy (MTLE).

Methods: During the period 2004–2010 61 patients were treated with SAHE for MTLE. Mean post-operative follow-up was 5.3 years. At the last postsurgical visit, 43 (70.5 %) patients were assessed as Engel Class I, six (9.8 %) Class II, nine (14.8 %) Class III and three (4.9 %) Class IV.

41 patients underwent neuropsychological assessment preoperatively and 12 months after surgery. Patients were tested in two sessions on two consecutive days. On the first day, a psychological interview and the Wechsler Adult Intelligence Scale – Revised (WAIS-R) was performed. On the second day, memory function was assessed by the Wechsler Memory Scale – Revised (WMS-R).

Results: SAHE did not cause memory impairments; neuropsychological outcomes were not affected in any parameters and right-sided operated patients significantly improved in Global MQ, Verbal MQ and Delayed Recall.

SAHE was complicated by four intracranial hematomas. One of them caused acute hydrocephalus and was treated by shunting and resolved without sequel. After SAHE, open epilepsy surgery and re-thermo lesions in three and two patients, respectively (8.2 %) was performed. There were two cases of meningitis which required antibiotic treatment. In six patients psychiatric disorders developed and one of these committed suicide due to postoperative depression.

Conclusion: SAHE provided high rate of cure with low morbidity and can be considered as an alternative therapy for MTLE.

#220

Changes in intracerebral EEG connectivity during VNS

Romain Carron (1), Francesca Bonini (2), Jean Régis (1), Fabrice Wendling (3), Fabrice Bartolomei (4)

1. *Functional and stereotactic neurosurgery, La Timone University Hospital, Marseille, France*

2. *Department of Epilepsy and Clinical Neurophysiology, La Timone University Hospital, Marseille, France*

3. *Neurosciences department, Rennes University France, Rennes, France*

4. *Department of Clinical Neurophysiology and Epilepsy, La Timone University Hospital, Marseille, France*

Introduction: Vagal nerve stimulation (VNS) is a neurostimulation technique that has been proved to be efficient in a significant number of cases of patients with drug resistant epilepsies. Its mode of action is still poorly understood and it is not clear which epileptic patients actually prove the best candidates for this therapy.

Methods: We recently had the opportunity to explore using SEEG (depth electrodes) a 24 year-old male patient with a severe drug-resistant temporo-perisylvian epilepsy. He had a history of type 1 neurofibromatosis with a normal brain MRI. His seizure started with a loss of consciousness associated with staring, swallowing and hypersalivation, followed by apnea and bilateral tonic contraction of superior limbs. VNS was implanted first before any invasive intracerebral recordings. The patient did not show any improvement (no seizure reduction) following VNS regardless of the parameters and duration of follow-up post-implantation. A predominantly right temporo-operculo-insular exploration was performed with a total 12 electrodes (10 right and 2 left). During SEEG we studied the effect of VNS on SEEG signals synchrony. Signals derived from 29 bipolar derivations from the temporo-mesial, opercular, insular prefrontal and parietal cortices were tested while the VNS stimulation was on (30Hz, 1-2 mA) and off.

Results: We found that synchronization of signals (using non linear correlation, h^2 method) significantly increased during the ON period relative to the OFF periods. This increased synchrony affected some channels exploring the prefrontal, parietal and insular cortices. No changes were found in the mesial temporal structures from where seizures started in this patient.

Conclusion: To our knowledge, this is the first report of functional connectivity changes observed during VNS. The increased synchronization (instead of decrease) and regional variability of the effect could explain the failure of VNS in this patient. This study could pave the way for a better understanding of VNS mechanisms of action and be paramount for a better screening of the type of epileptic patients proving the best candidates for VNS therapy. Additional data are being collected from other VNS patients.

#246

DBS of ANT for Epilepsy – Long Term Follow-up

Alexandre Rainha Campos (1), Inês Cordeiro (2), Carla Bentes (2), Ana Rita Peralta (2), José Pimentel (2), António Gonçalves-Ferreira (1)

1. Neurosurgery, University Hospital Santa Maria, Lisbon, Portugal

2. Neurology, University Hospital Santa Maria, Lisbon, Portugal

Submitter: Mr Campos Alexandre (PT)

Palliative epilepsy surgery is a modality usually used when there is no other more “definitive option” to offer or, in some cases, when patient don't want to take the risks of a resective surgery. In recent years, bilateral Deep Brain Stimulation (DBS) of the Anterior Nucleus of Thalamus (ANT) appeared as a new strategy to treat refractory cases of epilepsy.

Our group of Epilepsy Surgery at the Neurosciences Department of the University Hospital Santa Maria in Lisbon, Portugal, started implanting electrodes for DBS of the ANT in January 2011. We've latter enrolled the first 4 cases retrospectively and the last 5 prospectively in an observational European study. These 9 patients (7 females, 2 males) were operated between January 2011 and July 2013, with a median time of epilepsy until implant of 26 years (8-37), median number of seizures of 20,9/month (3-39), ictal onset zone in temporal zone alone in 6, and plus one or more lobe in 3, all taking more than 3 antiepileptic drugs and 1 with a previous VNS implanted and 2 with prior resective surgeries.

In 7 patients, after all the usual epilepsy surgery workup, we couldn't offer any other option but some neuromodulation modality and 2 refused the risks of a resective surgery.

Electrodes were all placed with Leksell® stereotactic frame with FrameLink®, Medtronic® used for planning targets and trajectories. In 4 patients we used Md.3389 and in 5 Md.3387 electrodes. The transventricular approach was used in 5 patients, extraventricular in 2 and mixed in 1. The baseline DBS parameters were: 145 Hz, 5 volts, 90 msec with 1 minute ON and 5 minutes OFF. Some parameters were changed latter to try to improve outcome.

In 6 patients it occurred a seizure reduction both in frequency and intensity. Changes in the Seizure Severity and Quality of Life were obtained in all patients that reported shorter seizures with less time of recovery and milder seizures. Major adverse events were: depression in 4/9 patients; DBS induced seizures/auras in 2; leads displacement in 1; pain over the IPG in 1.

Comments: Improvement of seizure frequency on 2/3 of the patients and general improvement of the seizure severity; subjective improvement in the majority of the patients; few major adverse events occurred, most of them solved. Introducing some changing of DBS parameters, further reduction of seizures was obtained. Still we cannot provide a good protocol because greater number of patients is required to do this. The best ANT-DBS candidates are still to define.

1.2.4 Pain

#41

Relation of effective stimulation settings and motor threshold in motor cortex stimulation

Philipp J Slotty (1), Walleed Dabbas (1), Christopher R Honey (1)
 1. Division of Neurosurgery, Vancouver General Hospital, Vancouver, BC, Canada

Submitter: Mr Slotty Philipp J (CA)

Introduction: Motor cortex stimulation can be effective in the treatment of neuropathic pain disorders. Unfortunately, no widely accepted programming guidelines exist. Large differences in response to MCS can be seen between patients and within individual patients at different times. These variations can be reduced by studying each individual's stimulation intensity as a percentage of their motor threshold (intensity required to cause a motor contraction) rather than as a raw voltage or current. We propose that effective stimulation voltage can be determined as a percentage of motor threshold.

Methods: 21 data sets of 7 patients being treated with motor cortex stimulation for chronic neuropathic pain were retrospectively analyzed. Patients were classified as successfully or unsuccessfully treated by the mutual agreement of the patient and their physician. Stimulation parameters including the intensity of stimulation as a ratio of motor threshold were analyzed for significant differences between the outcome groups (Mann-Whitney-U test).

Results: Out of 21 measurement 15 were stratified as successful and 6 as unsuccessful. There was no significant difference ($p=0.235$) between the mean voltage in the successful (5.06 V) and unsuccessful (4.26 V) settings. When the stimulation intensity was measured as a percentage of each individual's motor threshold, there was a significant difference ($p=0.029$) between the successful (77.6%) and unsuccessful (60.1%) therapies.

Conclusion: When considering MCS parameters, the absolute value of the voltage (or current) is probably far less important than the degree to which the stimulation is influencing the motor cortex. We propose that the motor threshold percentage (MTP) represents an important parameter that measures the degree to which MCS may be affecting the motor cortex. In our retrospective cohort, it appeared that $MTP > 70\%$ was required for effective pain relief. Targeting therapy to a MTP level may speed initial programming, allow more consistent longitudinal follow-up and be a basis for a standardized programming paradigm.

#138

SACRAL NERVE ROOTE STIMULATION (SNRS) FOR THE CHRONIC PELVIC PAIN.

Emil Isagulyan (1), Vladimir Shabalov (1)

1. Functional Neurosurgery, N.N. Burdenko Neurosurgical Institute, Moscow, Russia

Submitter: Mr Isagulyan Emil (RU)**Objectives:** The aim of this retrospective observational study is to evaluate the efficacy SNRS for the chronic pelvic pain.**Methods:** Twenty one patients (6 male, 15 female, aged 19-71 years) underwent a trial of SNRS with temporary bipolar, quadripolar or octapolar percutaneous leads. From the trial, 4 of 21 patients were quantified that a poor results and were excluded from the study. 17 patients, who had pain relief > 50% were undergo permanent implantation of the neurostimulator (4 – posthysterectomic pain syndrome, 4 - post herpetic neuralgia, 5 – peripheral pudendopathy and in 4 cases posttraumatic pelvic pain, associated with spinal cord injury). In 9 cases pain was accompany with malfunction of pelvic organs (3 – retention, 4 incontinence and 2 cases with anorgasmia).

Patient pain score, drugs consumption, sleeping and working time and other parameters that influences on the quality of life was assessed by VAS. These results were compared before implant, after trial and in follow up from 6 to 36 months (average 18 months).

Results: Good results were obtained in almost all cases with positive trial. Absolute recovery was marked in 5 patients, good recovery in 9 patients and in 3 case results were considered as fluent. In all three cases with fluent result, patient hade very hi score psychogenic component of the pain (measured by verbal-color test). In all cases with dysfunction of pelvic organs was achieved positive tendency. In two cases from 3 with urine retention was achieved complete recovery. No serious adverse events have occurred. The one type of complication which happened during this study was a migration lead in three patients. The effect of stimulation has been completely restored after electrode replacement.**Conclusion:** Thereby we can conclude that in the right selected patients suffering from chronic pelvic pain, SNRS have been shown high effectiveness. That Efficiency like an efficiency of SCS, PNS or another type of Neuromodulation essentially depends on expressiveness of a psychogenic component of a severe chronic pain.

#139

CENTRAL CORTEX STIMULATION (CCS) IN THE COMPLEX TREATMENT OF SEVERE PAIN

Vladimir Shabalov (1), Emil Isagulyan (1), Ekaterina Salova (2), Alexei Tomskiy (3)

1. *Functional Neurosurgery, N.N. Burdenko Neurosurgical Institute, Moscow, Russia*

2. *Anesthesiology, N.N.Burdenko Institute of Neurosurgery of RAMS, Moscow, Russia*

3. *Functional Neurosurgery, N.N.Burdenko Institute of Neurosurgery of RAMS, Moscow, Russia*

Submitter: Mr Isagulyan Emil (RU)

Objectives: Our goal was to present the possibilities of CCS in the complex treatment of severe neuropathic pain.

Methods: 23 patients (12 males and 11 females, aged 29 - 56 years) were undergone to implantation of epidural electrodes over the central sulcus region since 2005 until 2011 years. Six patients had facial anesthesia dolorosa related to different procedures on the trigeminal nerve branches, 6 patients had severe deafferentation pain in the arm due to traumatic brachial plexus injury, 4 patients suffered from poststroke pain syndrome (PSP). Another 6 patients had phantom limb pain. Finally one patient (female) suffered from referred pain due to traumatic spinal cord injury (C6 fracture) with tetraparesis. In case of positive trial stimulation in 20 of them the neurostimulator was subcutaneously implanted. Repetitive transcranial magnetic stimulation (rTMS) of the contralateral to the pain territory central cortex was performed in all patients as a trial preoperative test. Pain intensity was evaluated with Pain and Quality of Life Card (PQLC) based on 10-point Visual Analog Scale (VAS). In 17 patients this test was positive.

Results: In all these 17 patients good outcomes were achieved, both in immediate postoperative period and in long-term (up to 48 month) follow-up. Pain had improved by 35 to 70% in comparison with baseline. All 17 patients have stopped to use opiates. Loss of CSC effect was observed several months later in 3 cases: one patient with traumatic spinal cord injury and two patients with complete avulsion of brachial plexus. In these cases patients has not answered on rTMS, but insist on trial test with implanted leads.

Conclusion: Central cortex stimulation is effective technique for the treatment of severe neuropathic pain. Preoperative rTMS outcomes in general correspond to ones of chronic MCS. In some cases, such as phantom limb pain or anesthesia dolorosa, patients hasn't any alternative treatment options. Thereby, in these medical resistant cases, CSC could be method of choice.

#167

DRUG-ENHANCED SPINAL CORD STIMULATION IN NEUROPATHIC PAIN: LONG TERM FOLLOW UP OF A TRANSLATIONAL BASED PILOT STUDY

Gastón Schechtmann (1), Jaleh Winter (1), Göran Lind (1)

1. Department of Neurosurgery and Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Submitter: Mr Schechtmann Gastón (SE)

Introduction: Spinal cord stimulation (SCS) is an effective surgical treatment in pharmacologically resistant neuropathic pain conditions. For many patients suffering from this type of chronic pain, SCS is in fact the last treatment option. However, 30 to 40% of well-selected patients fail to obtain satisfactory pain relief with SCS, and in some patients an initial good analgesic effect diminishes over time.

It has been shown that the underlying effect of SCS relies on the GABAergic and cholinergic systems in the spinal cord. Further, there is also evidence that intrathecal clonidine and baclofen modulate these systems as well in order to produce analgesia.

On the basis of experimental studies on SCS and intrathecal drugs in rats performed at Karolinska Institutet, a double-blind, placebo-controlled clinical trial was performed, demonstrating that clonidine and baclofen in low intrathecal doses also may enhance the analgesic effect of SCS in neuropathic pain patients as observed in animal models of neuropathic pain.

As a result of this clinical pilot study, 5 patients that reported significant pain reduction during the trial with SCS and i.t. injections of these drugs were treated with both SCS and concomitant continuous baclofen or clonidine infusion via a pump for intrathecal administration.

The aim of the present study was to investigate the pain relieving effect and side effects or complications in the long term follow up of these patients who have been treated with SCS and concomitant intrathecal baclofen or clonidine for about 60 months.

Methods: A written informed consent to participate, or to abandon whenever they wished, was obtained from all included patients in the study.

The long-term effect of the combined therapy of SCS and i.t. drug administration was evaluated using a structured interview by a pain specialist nurse. The patients were interrogated on the usefulness of "drug-enhanced SCS", side effects and changes in pain medication. The questionnaire also comprised global satisfaction with this therapy and quality of life.

Results: A long-term follow-up of a group of patients with combined SCS and clonidine or baclofen treatment revealed that they still enjoyed good pain relief, improving quality of life. However, the doses needed to be adjusted in order to obtain adequate pain relief.

Conclusion: A trial with i.t. clonidine and baclofen combined with SCS may be warrant in patients who do not obtain satisfactory pain relief with SCS alone or experienced a decreasing therapeutic effect.

Today, drug-enhanced SCS therapy appears to be useful only for a limited group of well selected patients. Also, this study demonstrates that an insufficient SCS effect in neuropathic pain patients may be considerably improved by intrathecal clonidine or baclofen administration, and that this enhanced effect persists for a long-time.

1.2.5 Neuroimaging

#51

Trigeminal nerve asymmetry in classic trigeminal neuralgia: evaluation by magnetic resonance imaging

Dusan Urgosik (1), Aaron Rulseh (2), Jiri Keller (2), Vojtech Svehlik (3), Daniel Horinek (4), Roman Liscak (1)

1. Stereotactic and radiation neurosurgery, Na Homolce Hospital, Prague, CzechRepublic

2. Department of radiology, Na Homolce Hospital, Prague, CzechRepublic

3. International Clinical Research Center, St. Anne's University Hospital, Brno, CzechRepublic

4. Department of Neurosurgery, Masaryk Hospital, J.E. Purkinje University, Usti nad Labem, CzechRepublic

Submitter: Mr Urgosik Dusan (CZ)

Introduction: Classic trigeminal neuralgia (CTN) is characterized by neuropathic facial pain that is not attributed to any underlying disorder, with the exception of neurovascular compression (NVC). We evaluated the volumes of affected and non-affected trigeminal nerves (TN) and the presence and type of NVC in large group of CTN subjects prior to gamma knife treatment (GKS) on MR images. Correlation between affected nerve volume and NVC, treatment outcome and demographic characteristics (age of patients, duration of disease) were explored.

Methods: We measured TN volumes along their course through the pontocerebellar cistern and NVC (including the type of NVC) in 84 subjects. MRI was acquired on 1 T Siemens Expert and 1.5 T Siemens Avanto scanners using CISS and 3D-T1 sequences with intravenous contrast. Volumetry was performed by manually tracing the contours in consistent grayscale using the auto setting mode in the Level dialog of Leksell GammaPlan v.10.1. Detailed examinations of pain relief and side effects after GKS (80 Gy, 4 mm collimator, single shot) applied to the root of the TN were performed. Statistical analyses (paired and two-sample t-tests, one-way analysis of variance (ANOVA), linear model, the Bonferroni correction for multiple comparisons) were calculated in R.

Results: TN volume on the affected side was significantly smaller (34.9 ± 14 mm³ (SD)) than the volume of the unaffected side (41.9 ± 17 mm³, $p < 0.001$). NVC was detected in 71% of affected nerves, 52% of non-affected nerves, and in 31% of subjects bilaterally. No correlation between affected lower nerve volume and the presence and type NVC, treatment outcome or demographic data was detected.

Conclusion: In agreement with previous studies, there were statistically significant volume differences between affected and unaffected TN in CTN patients. However, statistically significant correlation between the duration of pain, functional changes of the affected TN after GKS and TN volume were not found. Our results suggest that NVC may trigger CTN in susceptible subjects but is not a reliable disease marker. Lower TN volume appears to manifest independently of NVC, and may represent nerve asymmetry rather than atrophy.

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#172

What You See is What You Get:**Lead Location Within Deep Brain Structures is Accurately Depicted by Stereotactic MRI**

Jonathan HYAM (1), Harith AKRAM (2), Marwan HARIZ (3), Ludvic ZRINZO (4)

1. Victor Horsley Department of Neurosurgery, National hospital for Neurology & Neurosurgery, Queen Square, London, UnitedKingdom

2. Unit of Functional Neurosurgery, National hospital for Neurology & Neurosurgery, Queen Square, London, UnitedKingdom

3. Unit of Functional Neurosurgery, National Hospital for Neurology & Neurosurgery, Queen Square, London, UnitedKingdom

4. Victor Horsley Department of Neurosurgery, National Hospital for Neurology & Neurosurgery, Queen Square, London, UnitedKingdom

Submitter: Mr HYAM Jonathan (GB)

Introduction: MRI-verified deep brain electrode implantation relies on correct interpretation of stereotactic MR imaging documenting lead location in relation to the visible anatomical target. Phantom studies have demonstrated that MRI provides a reliable marker of lead location. However, it has been suggested that local signal distortion from the electrode itself renders MRI an unreliable method of localisation in vivo. The aim of this study was to compare electrode location on MRI with subsequent location of its brain track after its removal, without concern for a putative electrode artifact.

Methods: Patients undergoing subthalamic or pallidal deep brain stimulation using a Leksell frame and MRI-verified approach were studied. Infection or suboptimal efficacy required lead removal. Re-implantation was performed at a later date using the same technique. Post-implantation stereotactic T2-weighted or proton density MR images (1.5T, specific absorption rate 0.4W/kg) from the first procedure were analysed using FrameLink software (Medtronic Inc, MN, USA). The lateral (x) and anteroposterior (y) distances from the midcommissural point to the centre of the electrode hypointensity were recorded at the level of the anterior commissure-posterior commissure (AC-PC) plane (vertical (z) = 0, for pallidal electrode) or below (z = -4, for subthalamic electrode). On the stereotactic MRI prior to the second procedure, the x and y distances from centre of the electrode track to the midcommissural point were independently recorded. The vectorial distance from the centre of the lead hypointensity to the centre of its tract was calculated using the equation: Distance = $\sqrt{(sq(x) + sq(y))}$

Results: Sixteen electrode tracks were studied in ten patients. Mean differences between electrode artefact location and electrode track location were as follows: in x coordinate 0.36mm±0.24 (range 0.11–0.94); in y coordinate 0.55mm±0.26 (range 0.11–0.87). Mean vectorial distance was 0.71mm±0.23 (range 0.33–1.07).

Conclusion: In this series, the stereotactic distance between lead location and subsequent brain track location on MRI was small. The mean discrepancy was only two-thirds of the width of a DBS electrode and well within the margin error of the method used to make the calculations. This suggests that the lead hypointensity seen on post-implantation MRI is indeed an accurate representation of its real location within deep brain structures.

#188

Targeting of the ventro-intermediate nucleus for Gamma Knife surgery purposes using high-field 7 Tesla MRI: a pilot in vivo study on healthy young subjects

Constantin Tuleasca (1), Elena Najdenovska (1), José Rebelo Ferreira Marques (2), Francois Vingerhoets (3), Jean-Philippe Thiran (4), Meritxell Bach Cuadra (5), Marc Levivier (1)

1. Neurosurgery Service and Gamma Knife Center, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

2. (CIBM), Centre d'Imagerie Biomedicale, Lausanne, Switzerland

3. Neurology Service, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

4. Laboratory of Transmission Signal (LTS-5), Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland

5. Medical Image Analysis Laboratory, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Submitter: Mr Tuleasca Constantin (CH)

Introduction: Gamma Knife surgery (GKS) is a non-invasive neurosurgical stereotactic procedure, increasingly used as an alternative to open functional procedures. This includes the targeting of the ventro-intermediate (Vim) nucleus of the thalamus for tremor. We currently perform an indirect targeting, using the “quadrilatere of Guiot”, as the Vim nucleus is not visible on current 3 Tesla (T) MRI acquisitions. The primary objective of the current study was to enhance anatomic imaging for Vim GKS using high-field (7 T) MRI, with the aim of refining the visualisation and precision of anatomical targeting.

Methods: Five young healthy subjects (mean age 23 years) were scanned both on 3 and 7 T MRI in Lausanne University Hospital (CHUV) and Center for Biomedical Imaging (CIBM). Classical T1-weighted MPRAGE, T2 CISS sequences (replacing former ventriculography) and diffusion tensor imaging were acquired at 3T. We obtained high-resolution susceptibility weighted images (SWI) at 7T for the visualization of thalamic subparts. SWI was further integrated for the first time into Leksell Gamma Plan® (LGP) software and co-registered with the 3T images. A simulation of targeting of the Vim was done using the “quadrilatere of Guiot” methodology on the 3T images. Furthermore, a correlation with the position of the found target on SWI was performed. The atlas of Morel et al. was used to confirm the findings on a detailed computer analysis outside LGP (by using 3D Slicer and Mint Softwares).

Results: The use of SWI provided a superior resolution and improved image contrast within the central gray matter. This allowed visualization and direct delineation of groups of thalamic nuclei in vivo, including the Vim. The position of the target, as assessed with the “quadrilatere of Guiot” method on 3 T, perfectly matched with the supposed one of the Vim on the SWI. Furthermore, a 3-dimensional model of the Vim target area was created on the basis of 3T and 7T images.

Conclusion: This is the first report of the integration of SWI high-field MRI into the LGP in healthy subjects and in one patient treated GKS Vim thalamotomy. This approach aims at the improvement of targeting validation and further direct targeting of the Vim in tremor. The anatomical correlation between the direct visualization on 7T and the current targeting methods on 3T seems to show a very good anatomical matching. Further studies are needed to have statistically significant results, to perform a clinical validation and to have realistic acquisitions (e.g. elderly)

#267

Can we rely on susceptibility weighted imaging (SWI) for identification of the STN in DBS surgery?

M. Bot¹, MD, L. Bour², PhD, R.M.A. de Bie², MD PhD, P.R. Schuurman¹, MD PhD, P. van den Munckhof, MD¹ PhD
 Dept of Neurosurgery¹ Academic Medical Center, Amsterdam, NL; Dept of Neurology and Neurophysiology² Academic Medical Center, Amsterdam, NL;

Objectives: To determine the correspondence between intra-operative electrophysiological activity of the subthalamic nucleus (STN) and the nucleus' representation on different MRI sequences used for deep brain stimulation (DBS) target planning.

Background: Susceptibility weighted imaging (SWI) is nowadays considered to offer significantly improved visibility of the STN, as compared to traditional T2-weighted (T2W) imaging. However, it is unknown whether the nucleus' representation on SWI corresponds with the neurophysiological location of the STN.

Methods: At stereotactic target depth, microelectrode recordings (MER) of typical STN neuronal activity were mapped on three different pre-operative MRI sequences: 1.5-Tesla SWI, 1.5-Tesla T2W and 3-Tesla T2W. For each MRI sequence, it was determined whether the MER signal was situated inside or outside the contour of the STN.

Results: 198 MER tracks in 34 patients were evaluated. 184 tracks (92.9%) measured typical electrophysiological STN activity. MER activity was situated more consistently inside STN-contour representation on 1.5-Tesla T2 and 3-Tesla T2 compared to SWI (73.5% and 79.6% vs. 57.7%). In addition, electrophysiological STN activity outside the anatomical region was more frequently seen on SWI compared to 1.5-Tesla T2 and 3-Tesla weighted MRI (16.3% vs 2.0% and 0.0%). Especially lateral (46.1%) and anterior (46.1%) tracks measured electrophysiological activity outside the hypointense contour thought to represent STN on SWI.

Conclusion: Anterior and lateral borders of hypointense contours thought to represent STN on SWI may not correctly correspond with electrophysiological STN borders. The contour of the STN on SWI tends to represent the medial parts of the nucleus more correctly compared to neurophysiological determined borders. When targeting the dorsolateral sensorimotor part of the STN, this "medial tendency" of the SWI should be taken into account.

1.2.9 Radiosurgery

#218

How spatially accurate is a mono-isocentric shot with Leksell Gamma Knife at the end of the procedure ? Results of a series of 85 patients.

Romain Carron (1), Michel Lefranc (2), Antoine Dorenlot (3), Denis Pocheron (3), Pierre-Yves Borius (1), Jean Régis (4)

1. Functional and stereotactic neurosurgery, La Timone University Hospital, Marseille, France

2. Functional and stereotactic neurosurgery, La Timone University Hospital, Marseille/ Amiens, France

3. Gammaknife Unit (Medical Physicist), La Timone University Hospital, Marseille, France

4. Functional and stereotactic neurosurgery (Head of), La Timone University Hospital, Marseille, France

Introduction: It is a classical notion in functional and stereotactic neurosurgery that the alleged mechanical precision provided by the manufacturer of any device represents only one of the parameters impacting upon the final accuracy. Every step from the frame application, the acquisition of the images, their definition and transfer into the stereotactic space to the delivery of dose, is likely to deteriorate the final precision obtained at the very end of the procedure. The issue of the spatial accuracy, though often quantified with phantom, has not been much investigated in 'real life' conditions. However this is what really matters. Very few radiosurgical procedures rest upon the use of a unique isocenter and at a sufficient regimen of dose to induce an easily analyzable lesion on brain imaging, apart from Vim Gammaknife (GK) thalamotomy for tremor.

Methods: The authors took therefore advantage of the analysis of the imaging features of the lesion visible at one year follow-up in their population of Vim GK Thalamotomy for intractable essential or Parkinsonian tremor to analyze and quantify the degree of discrepancy between the set of coordinates (x,y,z) of the centre of the lesion and that of the prescribed isocenter. Patients were all treated according to the same protocol by the same operator -last author- (unique isocenter, 130Gy at the 100% isodose, positioned in the Vim nucleus of the thalamus). The center of the lesion was defined as the center of the spherical area of hypointensity identified on the postoperative T1-weighted imaging, which was fused with stereotactic images of the treatment day with LeksellGammaPlan (LGP) 10.1.1 software. The quantification of the discrepancy was expressed in mm as Δx , Δy and Δz and in terms of mean vectorial error (MVE). A certain amount of inaccuracy being ascribable to the fusion process between the stereotactic images and the non-stereotactic follow-up ones, the authors endeavored to approximate the magnitude of error related to this "coregistration" process by measuring the discrepancy at the level of two landmarks (AC and PC) in terms of Δx , Δy and Δz and MVE.

Results: For most patients, the follow-up imaging was performed in the appropriate format (square pixels) rendering it compatible with LGP 10.1.1 software. Thus could it be fused with the stereotactic images of the treatment day. For 85 patients, the follow-up demonstrated a characteristic nodular lesion appearing as an area of hypo-intensity on T1-weighted images whose centre was easily and unequivocally determined. The measured discrepancy in mm (intended target vs lesion) were the following (mean (min;max;SD): $\Delta x = 0.38$ (0; 2.3;0.39); $\Delta y = 0.36$ (0;2.3; 0.37); $\Delta z = 0.67$ (0;1.9;0.37) with a mean vectorial error of 0.98 mm ranging from 0.1 to 2.73 (SD=0.55). The mean vectorial error related to the fusion process for AC-PC was 0.50 mm (0;1.86; SD:0.33). A final "weighted" mean error incorporating the fusion process was estimated at 0.63 mm.

Conclusion: This study is, to our knowledge, the first demonstration of the inframillimetric accuracy of Gammaknife radiosurgery in "real-life" conditions and let emphasis upon the need of a rigorous methodology for every single step of the procedure. Any extrapolation of these results for other radiosurgical devices which are based on different technology and imaging procedures should be made with great caution.

1.2.10 Experimental studies

#20

Deep brain stimulation of the rat subthalamic nucleus induced inhibition of median raphe serotonergic and dopaminergic neurotransmission

Ersoy Kocabicak (1), Ali Jahanshahi (2), Lisa Schönfeld (3), Sarah-Anna Heschem (2), Yasin Temel (2,4), Sonny K.H Tan (5)

1. Department of Neurosurgery, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

2. Department of Neuroscience, Maastricht University Medical Center, Maastricht, Netherlands

3. Department of Morphology, Hasselt University, Diepenbeek, Belgium

4. Department of Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

5. Department of Neurosurgery, University Hospital RWTH, Aachen, Germany

Introduction: DBS of the subthalamic nucleus (STN) relieves motor dysfunction in advanced Parkinson's disease (PD). However, STN DBS treated patients can experience unpleasant and debilitating psychiatric side effects such as depression and impulsivity. The neural basis of these psychiatric effects has been linked to a dysfunction of 5-hydroxytryptamine (5-HT, serotonin) neurotransmission. STN DBS inhibited activity of 5-HT cell bodies in the dorsal raphe nucleus (DRN). Another important 5-HT source is located in the median raphe nucleus (MRN), which also contains a population of dopamine neurons. The effects of STN DBS on the MRN are unknown. Here, we test the hypothesis that STN DBS reduces 5-HT and dopaminergic function in the MRN, which may contribute to the psychiatric side effects of STN stimulation.

Methods: Bilateral STN DBS was applied in a freely moving rat model. Following STN DBS, rats were sacrificed and the brains were processed for c-Fos, 5-HT and tyrosine hydroxylase (TH) immunohistochemistry.

Results: We found that STN DBS significantly lowered c-Fos expression compared to non-stimulated controls indicating reduced neuronal activity. Moreover, the mean optical density values of 5-HT and TH cells in the MRN was significantly lower compared to controls.

Conclusion: These results show that STN DBS inhibits 5-HT and dopamine neurotransmission in the MRN.

#130

Ventral tegmental area lesion-induced ultrasonic vocalization phenotype reversed by high-frequency stimulation of the medial forebrain bundle in rodents: indication of non-dopaminergic mechanisms

Luciano L Furlanetti (1), Timo S Spehl (2), Lars Frings (2), Friederike Braun (2), Marisa Ferch (2), Philipp T Meyer (2), Máté D Döbrössy (1), Volker A Coenen (1)

1. Dept. of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Freiburg, Germany

2. Dept. of Nuclear Medicine, Freiburg University Medical Center, Freiburg, Germany

Introduction: DBS of the medial forebrain bundle (MFB) has been tested clinically in major depressive disorder patients with rapid and long-term reduction of symptoms. However, the mechanisms and neurobiological outcome of the stimulation are not known. In the context of chronic and continuous bilateral high frequency stimulation (HFS) of the MFB, the current study looked at the impact of lesioning the ascending dopaminergic pathway originating from the ventral tegmental area in behavioral and global cerebral glucose metabolism.

Methods: Sprague-Dawley female rats were given bilateral injection of 6-OHDA into the VTA (VTA-lx, n=8) or left unlesioned (Control, n=8). Later, all animals received bilateral microelectrode implantation into the MFB followed by chronic continuous HFS for 3 weeks. Behavior assessments including ultrasonic vocalization (USV), and F-18-FDG-PET imaging were performed along the experiment, aiming to evaluate the impact of mesolimbic dopamine depletion and regional cerebral glucose metabolism on MFB-HFS outcome. Post-mortem histological analysis was carried out. Comparison of regional glucose-metabolism between pre-stimulation and post-stimulation scans was performed by statistical parametric mapping (SPM) with a threshold of $p < 0.05$, uncorrected, > 20 continuous voxels.

Results: Pre-stimulation baseline testing of the VTA-lx animals showed a higher incidence of USV in the 22 kHz range, and lower incidence of USV in the 50kHz range compared to Controls. MFB-HFS induced a temporary and mild weight drop in the Controls, but had little impact in the VTA-Lx group. HFS reduced the incidence of USV in the 22 kHz range, making it similar to the Control levels; conversely, HFS increased USV in the 50 kHz range in both groups as well. Motor activity increased during the initial 72 hours of stimulation, and food intake decreased by 25% up to 2 weeks post MFB-HFS only in the control group. HFS did not influence performance on either a test of anxiety or behavioral despair. Following stimulation, PET scan revealed a regional increase in brain glucose metabolism in the left entorhinal cortex in the VTA-lx group, whereas the control group showed primarily a decrease of glucose metabolism in widespread areas of the cortex. Amongst the Controls, MFB-HFS led to a distinct decrease in metabolism of the entorhinal cortex area, as opposed to the VTA-lx group.

Conclusion: Bilateral continuous chronic MFB-HFS is feasible and safe. MFB-HFS results in temporary increase in exploration, which could explain the initial weight loss and decreased food intake. Animals with bilateral VTA lesions showed mitigated response to the HFS induced weight loss. However, the VTA lesioned animals – similar to the Controls - reduced the negative-affect (22kHz) and increased the positive-affect (50 kHz) USVs post-HFS, suggesting that non-dopaminergic mechanisms are also at play. The platform, including the PET imaging, represents a powerful tool for further preclinical investigation of MFB stimulation in the treatment of depression.

#131

Electrophysiological correlates of auditory change detection: A simultaneous depth and scalp EEG study

Anne-Kathrin Beck (1), Götz Lütjens (1), Hans Heissler (1), Kerstin Schwabe (1), Reinhard Dengler (2), Joachim Kurt Krauss (1), Pascale Sandmann (2)

1. Neurosurgery, Hannover Medical School, Hannover, Germany

2. Neurology, Hannover Medical School, Hannover, Germany

Introduction: Attentive monitoring of environmental stimuli is fundamental for efficient detection of relevant stimuli and well investigated for cortical regions. Subcortical network circuitry and the involvement of these structures in the context of detection of relevant stimuli, involuntary attention and distractibility, however, is not well understood. The P300 component is frequently used in electroencephalographic (EEG) studies as a measure for attentional and cognitive functions and is supposed to give further insight to context-specific processes of subcortical structures.

Methods: In this ongoing study, simultaneous recordings of local field potentials (LFPs) and event-related potentials (ERPs) from scalp EEG were obtained in six patients (mean age= 63.8±11 years) undergoing deep brain stimulation (DBS). These patients were implanted bilaterally with quadripolar electrodes in the subthalamic nucleus (STN; n=2; Parkinson disease), the thalamic ventral intermediate nucleus (VIM; n=2; essential tremor and cervical dystonia), or the globus pallidus internus (GPi; n=2; segmental dystonia and Parkinson disease). Within five days after surgery, patients performed an auditory three-class oddball paradigm with externalized DBS electrodes. ERPs from scalp and DBS electrodes were analyzed upon presentation of one frequent standard stimulus (900 Hz; 72%) and two infrequent stimuli, either being a relevant (1200 Hz; 14%) or a distractor (600 Hz; 14%) stimulus. Stimuli were presented for 62 ms with an interstimulus interval of 800 to 1200 ms. The patients were asked to press a button to the relevant stimulus.

Results: Analysis reveals high accuracy in all six patients (86.9%±10.7). Preliminary EEG results show a P300 component over parietal regions that was largest upon presentation of target stimuli compared with distractor and standard stimuli. A similar P300-like component was also found in depth recordings, suggesting stimulus-specific responses of subcortical structures. Here, STN showed shorter latencies and larger amplitudes compared to GPi or Vim.

Conclusion: The P300 reflects attentional processes that require stimulus detection and discrimination. The present results suggest that, in particular, the STN may play a pivotal role in context-specific processes.

#164

Subthalamic nucleus high frequency stimulation reduces – almost immediately - primary sensorimotor and prefrontal dorsolateral cortical activity whatever the patient is at rest or performing a motor task: a fNIRS study

Michel Lefranc (1), Mahdi Mahmoudzadeh (2), Melissa Tir (3), Pierre Krystkowiak (4), Fabrice Wallois (2)

1. Neurosurgery, CHU Amiens, Amiens, France

2. Inserm U1105, GRAMFC laboratoire de neurophysiologie UFR médecine, Université Picardie Jules Vernes - CHU Amiens, Amiens, France

3. Service de Neurologie, CHU Amiens, Amiens, France

4. EA 4559 Laboratoire de Neurosciences Fonctionnelles et pathologie (LNFP) Université de Picardie Jules Vernes - Service de Neurologie, Université Picardie Jules Vernes - CHU Amiens, Amiens, France

Introduction: STN-DBS is an effective treatment for idiopathic Parkinson disease. However, the efficacy of STN-DBS relies on unclear mechanisms. In this study, using optical imaging, we evaluated the cortical hemodynamic changes induced by STN-DBS.

Methods: We performed a functional optical imaging study using Near-InfraRed Spectroscopy (fNIRS) in 7 parkinsonian patients after STN-DBS. We measured bilateral local cortical hemodynamic changes under “On” and “Off” stimulation conditions at rest and during a motor task (hand movement). Relative concentration changes of oxyhaemoglobin (HbO), deoxyhaemoglobin (dHb), and total Haemoglobin (tHb) were continuously analysed.

Results: In STN-DBS “off” condition Oxy-Hb and tHb increased immediately in regard of motor and pre motor dorsolateral cortical area after the onset of the motor task. In STN-DBS “on” condition without realisation of any movement, a decrease in HbO and tHb within the 5 first seconds of stimulation, maintained during all the time of stimulation is objectified in regard of sensori-motor area and dorsolateral cortex for all patients. During motor task and STN-DBS “On” condition, a specific increase of HbO -ie cortical activation- of motor cortex and pre-motor cortex is objectivized whereas other cortical regions still presented decrease of HbO in 5 patients. There was a significant reduction of the increase of HbO during the motor task in front of “off” STN-DBS condition for all patients.

Conclusion: This study shows that fNIRS is an efficient tool to measure local real time cortical hemodynamic variation during STN-DBS. It provides new arguments in favour of STN-DBS main cortical effect, which is to reduce regional cerebral blood flow in the primary sensorimotor and premotor dorsolateral cortex areas. Our study advocates that STN-DBS neuromodulation output is always the same whatever is the cortical activity and appears almost immediately after that stimulation has started.

#193

Lesions of cholinergic neurons in the anterior or posterior pedunclopontine nucleus in rats: effect on motor behaviour and neuronal network activity in the basal ganglia motor loop

Xingxing Jin (1), Kerstin Schwabe (1), Joachim K Krauss (1), Mesbah Alam (1)
1. Department of Neurosurgery, Hannover Medical School, Hannover, Germany

Objective: To investigate the effect of anterior or posterior cholinergic lesions of the pedunclopontine nucleus (PPN) in on gait-related motor behaviour, and on neuronal network activity of the PPN area and basal ganglia (BG) motor loop. Loss of cholinergic neurons in the mesencephalic locomotor region, comprising the PPN and the cuneiform nucleus (CnF), are related to gait disturbances in late stage Parkinson's disease (PD).

Methods: Anterior (n=8), posterior (n=8) PPN lesions or sham lesions (n=6) were induced by stereotaxic microinjection of the cholinergic toxin AF64A or vehicle in male Sprague Dawley rats. First, locomotor activity (open field) and postural disturbances (rota rod) were assessed. Thereafter, single unit and oscillatory activity were measured in the non-lesioned area of the PPN, the CnF and the BG output region, the entopeduncular nucleus (EPN), with microelectrodes under urethane anaesthesia. Additionally, ECoG was recorded in the motor cortex.

Results: Anterior lesions disturbed rotarod behaviour, while posterior lesions reduced open field locomotion. Electrophysiological recording showed that the firing rate and firing patterns were significantly higher in the CnF after anterior PPN lesions ($P<0.05$). Lesion of anterior and posterior PPN increased the coherence of beta oscillatory activity in motor cortex and EPN ($P<0.05$). Additionally, anterior PPN lesions decreased alpha oscillatory activity in the EPN and motor cortex ($P<0.05$).

Conclusion: Anterior or posterior PPN lesions had different impact on motor behaviour and neuronal firing parameters and its local field potentials coherences in the motor cortex. Loss of cholinergic neurons might contribute to the specific clinical phenomenology in late stage PD.

#195

Deep brain stimulation by 5-track microelectrode recordings causes no detectable by s-100b brain injury.

Marios Themistocleous (1), Christos Anagnostopoulos (1), Damianos Sakas (1)
1. Neurosurgery Department, Evangelismos General Hospital, Athens, Greece

Submitter: Mr Anagnostopoulos Christos (GR)

Introduction: Despite the wide acceptance of deep brain stimulation (DBS) there is considerable variability in the technical approach and several issues remain controversial. An important issue is whether the insertion of bilateral DBS electrodes or the use of multiple simultaneous tracts for the microelectrode recordings (MERs) is associated with a higher risk of brain damage such as hemorrhage, contusion or even damages not detectable by imaging. S-100b protein has been established as the most reliable, so far, biochemical marker of brain damage and a prognosticator of response to therapy. Moreover there is still debate about the necessity of the utilization of MERs or the use of 5 simultaneous tracks for the MERs. The aim of this study was to evaluate whether brain damage is caused during the passing of i) microrecording electrodes, ii) macrostimulation electrodes or iii) permanent stimulation electrodes and examine whether there is any relationship between the number of inserted electrodes and brain injury or morbidity.

Methods: Between 2009 and 2012, we implanted 117 DBS systems in 59 patients. Mean age of patients was 61,4 years (38-75 years) and the average duration of the disease was 15,1 years (7-29 years). We used an array of five microelectrodes separated by 2mm for MERs. Final location was selected according to the results of intraoperative MERs and macrostimulation. All patients underwent measurements of serum S-100b as follows: 1) prior to the operation 2) after the burr hole opening 3) after insertion of microrecording electrodes, 4) during macrostimulation, 5) at the end of the operation and 6) on the 1st postoperative day.

Results/conclusion: We found that S-100B protein was increased in only two cases. In all other cases, serum S-100b protein values remained within the normal range. No relationship was found between the number of inserted electrodes and brain damage such as hemorrhage, contusion or even damages not detectable by imaging.

#233

***In vitro* electrotaxis: low current densities attract neural precursor cells**

Lisa-Maria Schönfeld (1), Evi Lemmens (2), Ali Jahanshahi (3), Yasin Temel (3), Sven Hendrix (2)

1. Neuroscience & Biomedical Research Institute, Maastricht University & Hasselt University, Maastricht, Netherlands

2. Biomedical Research Institute, Hasselt University, Hasselt, Belgium

3. Neuroscience, Maastricht University, Maastricht, Netherlands

Introduction: Neural precursor cells (NPCs) have the capacity to sense and react to electrical fields (EFs) by migrating towards the cathode in vitro, a process called electrotaxis. Having the opportunity to steer NPC migration is interesting for in vivo studies aiming at regeneration, on both tissue- and functional levels. Before one is able to apply EFs to the brain to attract NPCs to a lesion site, the most efficient parameters of an EF to induce electrotaxis have to be determined. The present study assessed the effect of a number of varying current amplitudes on migration of NPCs in parallel.

Methods: SH-SY5Y cells were chronically exposed to an EF for a period of 24 h in a live cell imaging setup to visualize and evaluate cell migration. Electrical stimulation took place in a 12-well plate where SH-SY5Y cells adhered to the bottom of the wells. Stainless steel electrodes touching the bottom of the wells delivered monophasic cathodal current pulses with varying current densities of 5, 10, 20 and 40 μA at a fixed frequency of 50 Hz and a pulse width of 0.1 ms. Non-stimulated cells were used as a negative control to account for random patterns of cell migration during the stimulation period. Pictures taken during the 24 h stimulation period were stacked and the migration paths of individual cells were tracked manually using ImageJ. Displacement of SH-SY5Y cells towards the cathode was evaluated by assessing direction, velocity and distance of migration.

Results: Depending on the delivered current, SH-SY5Y cells showed increased displacement in the direction of the cathode. When compared to non-stimulated cells, cells stimulated with either 5 or 10 μA ended up significantly closer to the cathode after 24 h of EF exposure. Furthermore, exposure to the highest current density of 40 μA led to a visible decrease in cell viability.

In the current study, a number of clinically relevant stimulation parameters were applied chronically to SH-SY5Y cells, whereby usage of the lowest stimulation currents (e.g. 5 or 10 μA) was found most effective in inducing electrotactic migration. Studies assessing the effect of those stimulation parameters on cell phenotype and viability are still ongoing. Furthermore, the exact mechanism of electrotactic migration needs to be identified.

Conclusion: Knowledge about the most effective stimulation conditions to induce electrotaxis in NPCs will be transferred to a future in vivo study, where endogenous NPCs should be attracted towards a lesion site to yield functional recovery.

#168

Endothelial barrier dysfunction in temporal lobe epilepsy: preliminary results

Roel Haeren (1), Govert Hoogland (1), Olaf Schijns (1), Jim Dings (1), Kim Rijkers (1), Jo de Mey (2), Koo van Overbeeke (1), Paul Schiffers (2)

1. Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

2. Pharmacology, Maastricht University, Maastricht, Netherlands

Introduction: Blood-brain barrier dysfunction allows for alterations in brain homeostasis and neuronal functions. It has been shown that these alterations are involved in generating seizures. The vessel wall consists of three layers. The inner layer, called intima, is the most important barrier layer containing the endothelium, basement membrane and internal elastic lamina. The intima is surrounded by smooth muscle cells and the external elastic membrane, constituting the media layer. The outer layer or adventitia is made of connective tissue and includes the nerve supply. A disrupted blood-brain barrier and passage of proteins, like albumin, or electrolytes, like potassium, over the vessel layers can cause seizures and might be involved in epileptogenesis.

Aim of our study was to test the permeability of the inner endothelial cell layer in human temporal lobe epilepsy by using the vasoconstrictive neurotransmitter endothelin-1 (ET-1). ET-1 causes the smooth muscle cells to constrict by binding to the ET-A receptor.

Methods: Included neocortical samples were intraoperatively collected from drug-resistant temporal lobe epilepsy patients aged between 18 and 65 years, and eligible for respective surgery. Surgery encompasses an anterior temporal lobe resection with amygdalohippocampectomy. Small cortical arteries within these samples were isolated. In addition, middle cerebral arteries (MCA) derived from healthy 12 weeks old Wistar-Kyoto rats were isolated.

Arterial segments with a luminal diameter between 150-250nm) were mounted in an organ chamber between two glass cannulas and exposed to a constant distending pressure of 70 mmHg. Subsequently, increasing concentrations of ET-1 were applied extraluminally or intraluminally to the vessels and changes in arterial lumen diameter were recorded.

Results: Extraluminal application of ET-1 resulted in a concentration-dependent vasoconstriction in both, human neocortical small arteries and rat MCA. Interestingly, whereas in MCA controls, intraluminal application decreased the lumen diameter to a lesser degree than extraluminal application, human neocortical arteries were equally sensitive to intra- and extraluminal application.

Conclusion: ET-1 targets the surrounding smooth cells in a direct way when applied extraluminally, and needs to pass the endothelial barrier when applied intraluminally.

The observation that the sensitivity to extraluminal and intraluminal application of ET-1 was comparable in human neocortical small arteries suggests an altered endothelial barrier function in epilepsy patients.

#169

Vessel wall permeability in temporal lobe epilepsy

Roel Haeren (1), Denise Habets (2), Amanda van Vliet (2), Paul Schiffers (3), Olaf Schijns (4), Jim Dings (1), Jo de Mey (3), Marc van Zandvoort (5), Koo van Overbeeke (1), Hans Vink (6), Kim Rijkers (1)

1. Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

2. Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands

3. Pharmacology, Maastricht University, Maastricht, Netherlands

4. Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

5. Genetics and Cell biology, School for Cardiovascular diseases (CARIM), Maastricht University, Maastricht, Netherlands

6. Physiology, Maastricht University, Maastricht, Netherlands

Introduction: Blood-brain barrier dysfunction allows for alterations in brain homeostasis and neuronal functions. It has been shown that these alterations are involved in generating seizures. Recent studies have pointed out that leakage of nutrients and proteins are common in epileptic brain tissue. Aim of our study is to characterize blood-brain barrier permeability for dextran proteins in patients with temporal lobe epilepsy. Also, we provide a method of dextran penetration in the subsequent vessel wall layers, intima, media, and adventitia, respectively. Moreover, we include measurements of the intraluminal glycocalyx, which is a network of membrane-bound glycoproteins and proteoglycans that cover the luminal side of the endothelium. Glycocalyx measurements in epileptic neocortical arteries have not been performed before.

Methods: Included neocortical samples were derived from patients, between 18 and 65 years of age, with drug-resistant temporal lobe epilepsy eligible for respective surgery. Surgery encompasses an anterior temporal lobe resection with amygdalohippocampectomy.

Arterial segments were isolated from resected neocortical tissue and mounted in an organ chamber between two glass cannulas and exposed to a constant distending pressure of 70 mmHg. Subsequently, decreasing molecular weight dextran proteins were applied intraluminally. Using 2-photon microscopy, dextran proteins with various labels were imaged and possible extravasation of dextran proteins in the several arterial layers could be observed. Glycocalyx thickness was measured using high molecular weight labelled dextran proteins.

Results: The results of our experiment include 2-photon images of the arterial wall and lumen, showing the presence of intraluminal dextran proteins, the level of extravasation of these proteins of different molecular weights along the arterial wall, and glycocalyx thickness measurements. Correlation of our findings to clinical characteristics and degree of hippocampal sclerosis (Wyler grade) will be presented.

Conclusion: The in vivo measurement of vessel wall permeability in patients has always been a challenge. We have been able to demonstrate vessel wall permeability for dextran proteins using 2-photon microscopy. This technique also enabled us to determine the level of penetration of dextran along the different vessel wall layers. Furthermore, the results of our glycocalyx measurements in epileptic neocortical vessels will be included, which has not been presented before. Our findings of extravasation of dextran proteins in arteries derived from epileptic temporal lobe tissue evaluate the hypothesis of increased blood-brain permeability in epilepsy.

#280

Deep brain stimulation to restore memory loss?

Sarah Heschan^{a,d,*}, Ali Jahanshahi^{a,d}, Leewei Lim^{a,d}, Harry Steinbusch^{a,d}, Arjan Blokland^{c,d}, Yasin Temel^{a,b,d}

Department of ^a Neuroscience and ^bNeurosurgery, University of Maastricht, P.O. Box 616, 6200 MD Maastricht, the Netherlands

^cDepartment of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, the Netherlands

^dEuropean Graduate School of Neuroscience (Euron)

Introduction: DBS is a surgical treatment involving the implantation of electrodes, which give electrical impulses to specific parts of the brain. When structures of the memory circuitry are stimulated, DBS is thought to enhance neural activity and thus improves performance on memory tasks.

Methods: In the following study, we implanted bilateral electrodes at the site of the fornix, entorhinal cortex, CA1 subfield of the hippocampus, mammillothalamic tract and anterior nucleus of thalamus in order to detect which structures and which stimulation parameters provide beneficial effects in spatial memory. Rats were then tested in the Object Location Task with the following conditions: (i) with attachment of stimulation cable (off stimulation), and (ii) with DBS at various amplitudes (50 μ A, 100 μ A and 200 μ A), 100 μ s pulse width and 100 Hz or 10 Hz stimulation frequencies. Intraperitoneal scopolamine injections 30 min before the first trial was given to imitate memory impairment.

Results: DBS of the fornix reversed the scopolamine effects in high current densities and showed superior memory performance when compared to sham rats. With the most efficient stimulation parameter these rats did not show anxiety-like behaviour in the Open Field and Elevated Zero Maze, suggesting no potential side effects regarding anxiety levels or general motor activity. Immunohistochemical results suggest an increased neural activity in the CA1 region of the hippocampus. In another set of experiments DBS electrodes have been implanted in the fornix and microdialysis probes in the dorsal hippocampus. Acetylcholine levels, but not glutamate, seem to be elevated during DBS.

Conclusion: These findings suggest that one potential mechanism of action of the induced memory enhancement through fornix DBS might be due to increased acetylcholine release into the hippocampus.

2. Abstracts selected for Poster Presentations

2.1 Movement disorders

#9

Long-Term Outcomes of Bilateral Pallidal Stimulation for Primary Generalized Dystonia.

Michał Sobstyl (1), Mirosław Ząbek (1), Krzysztof Szczaluba (2), Tomasz Kmiec (3), Zbigniew Mossakowski (4), Karol Budohoski (1)

1. *Neurosurgical Department, Postgraduate Medical Center, Warsaw, Poland*

2. *Regional Center for Clinical Genetics and Modern Technologies, GenCentrum – Regional Center for Clinical Genetics and Modern Technologies, Kielce, Poland*

3. *Department of Children's Neurology and Epileptology, The Institute of Children's Health, Warsaw, Poland*

4. *Neurosurgical Department, Bródno Regional Hospital, Warsaw, Poland*

Introduction: Bilateral pallidal stimulation is an established surgical management of patients with primary generalized dystonia (PGD). The aim of this study is to present our long-term experience of bilateral pallidal stimulation in patients with PGD.

Methods: The study population is composed of 12 patients with the diagnosis of PGD (6 patients with DYT-1 positive PGD and 6 patients with DYT-1 negative PGD). The patients were operated on in general anesthesia. The stereotactic target - posteroventrolateral pallidum was calculated according to the midcommissural point derived from fusion of stereotactic computer tomography images with magnetic resonance images. The formal objective assessment included the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). The BFMDRS assessment was performed annually 5 years before and after when bilateral pallidal stimulation was switched on and compared to baseline scores.

Results: At the last follow-up visit (5 years after surgery) in 4 patients with DYT-1 positive PGD the functional and motor parts of the BFMDRS improved by 59 % and 66 % respectively when compared to baseline scores. In 4 patients with DYT-1 negative PGD the functional and motor parts of the BFMDRS improved by 60 % and 52 % 5 years postoperatively when compared to baseline scores. The hardware-related complications were quite common affecting 7 patients and included 4 breakages of DBS leads, 2 erosions located over the connector, 2 seromas at generators side and 2 rapid depletions of generators. 1 rapid generator depletion resulted in severe life-threatening status dystonicus.

Conclusion: Bilateral pallidal stimulation is an effective treatment in patients with PGD. The incidence of hardware-related complications is relatively high. Most of these complications can be managed successfully by repeated procedures and reduced by appropriate surgical technique. Any rapid aggravation of dystonia should be promptly reported to a treating center to avoid development of a possible life-threatening condition like severe status dystonicus

#23

Children's pallidal deep brain stimulation with torsion dystonia: case report.

Tatiana Tubaeva (1), Albert Sufianov (2), Vladimir Shabalov (3), Artur Biktimirov (1), Alexander Orlov (1), Sergey Churkin (1), Evgeniy Matveev (1)

1. *Functional neurosurgery, "Federal Centre of Neurosurgery", Tyumen, Russia, Tyumen, Russia*

2. *Neurosurgery, "Federal Centre of Neurosurgery", Tyumen, Russia, Tyumen, Russia*

3. *Functional Neurosurgery, "Federal Centre of Neurosurgery", Tyumen, Russia, Tyumen, Russia*

Introduction: Idiopathic torsion dystonia is a rare genetic condition which commonly affects children in the age group of 11 to 12 years. It begins in one part of the body and gradually begins to spread to other parts. Often these children cannot perform simple motor tasks and are usually confined to a wheelchair. Various conservative therapies can help in reducing the symptoms. That's why the treatment of the idiopathic torsion dystonia is a serious problem, because this disease in a short time can lead to disability and social exclusion of the child.

Case description: Patient K 2001 (date of birth) addressed to clinics with complaints of involuntary turning of the body back, turning of the head back and involuntary moving in the right and left hands, both legs. Anamnesis morbi: the child was born (second pregnancy, 40-41 weeks). The upgrowth till eight years was without peculiarities. His mother said that in eight years they noticed the signs of chirospasm in the right hand. The disease gradually progressed with time. From the beginning of the 2012 involuntary movements in the left hand and leg appeared. In several months involuntary turning of the body back and turning of the head back appeared. He was cured conservatory, without effect. In neurological status the patient has rough violation of the gait (the gait is impossible without remedial gesture), retrotorsion, retrocollis, retroshift, dystonia in the both legs and both hands. Unified scale dystonia (befor surgery) - 19,5. Scale evaluation of dystonic movements (R. Burke et.al.) – 15. 13.04.2013 the operation was fulfilled – implantation of the system for DBS GPI from two sides.

Results: Introducing and choice of primary stimulation program was done after 10 days after surgery. In 2-3 hours after switching on the stimulator the positive dynamics as improved gait, decrease in retortortion was seen. Unified scale dystonia (after surgery) – 6. Scale evaluation of dystonic movements (R. Burke et.al.) – 5

Conclusion: Children's pallidal deep brain stimulation is an effective method of correction of movement disorders in patients with idiopathic torsion dystonia. This method significantly improves the quality of life and social adaptation of patients.

#24

Combination of stereotactic radiofrequency lesion and neuromodulation techniques in treatment of Parkinson's disease

Evstafiy Melidi (1), Oxana Gavronina (1)

1. Functional neurosurgery department, Federal Neurosurgical Center, Novosibirsk, Russia

Objective: To set out the results of stereotactic radiofrequency lesion and neurostimulation of deep brain structures with the use of neurophysiologic navigation and microelectrode analysis in treatment of patients with Parkinson's disease.

Methods: Over a period of 2013 starting from the launch of the Functional division of the Federal Neurosurgical Center in Novosibirsk there were 127 patients with extrapyramidal pathology who underwent operative therapy. The main group consisted of 110 patients with lateralized form of Parkinson's disease to whom stereotactic destructions of deep brain structures were performed. There were 53 men and 57 women aged from 40 to 75 (middle age was $60,4 \pm 7,6$ years) with advanced stages (11-1V) according to Hoehn and Yahr scale and not less than 70% activities according to Schwab and England scale in "ON" period. 17 patients from the 2nd group were offered neurostimulation of deep brain structures for management of ambilateral semiology with such nosology. This group consisted of 11 men and 6 women aged from 49 to 66 (middle age was $58,5 \pm 5,1$ years). All operations were performed with the help of stereotactic frame of "Cosman-Roberts-Wells" construction and "Radionics" stereotactic planning system. Final verification of target's edges was performed with the help of "MicroGuide Pro" (AlphaOmega) intraoperational multi-channel system of microelectrode analysis.

Results: Unilateral radiofrequency lesion of basal ganglia were performed on 110 patients (63 ventrodorsal pallidotomy and 47 ventro-intermediate thalamotomy to stop dyskinesia, rigidity and tremor respectively). Intracerebral electrodes were stereotactically implanted into subthalamic nucleus region of 17 patients from both sides with single-step installation of Activa PC (Medtronic) nerve stimulator into the left infraclavicular area. One patient underwent unilateral pallidotomy 2 years ago. This allowed significant life quality improvement in this category of patients (PDQ-39 scale) by means of tremor and rigidity regress contralaterally at the average of 87% (UPDRS scale), dyskinesia decrease and reduction of fluctuation for 75%. In the group of neuromodulation associated with zero mortality there were neither perioperative complications, nor problems with implanted devices in the course of monitoring. There was a postsurgical depression medicamentally corrected after 1,5 months. Moderate increase of postural instability was marked in 2 of 17 patients (11%). Generally, in evaluation of the annual catamnesis, general improvement in more than a half of patients (77) who had chosen surgical methods of Parkinson's disease treatment should be mentioned: mental flexibility, the rate of speech sensing, visual and spatial reasoning.

Conclusion: It's known that the match of neurostimulation program directly depends on the accuracy of electrode placement that is why it's very important to use the electrical activity microelectrode registration system for individual mapping of the nuclear pinch length. Besides, the usage of neurophysiological navigation allows performing more safety stereotactic destructive operations on submillimeter accuracy level reaching the maximum clinical effect during decrease of complications risk for each patient.

#25

DEEP BRAIN STIMULATION FOR PARKINSON DISEASE IN KAZAKHSTAN

Serik Akshulakov (1), Chingiz Shashkin (1), Yerbol Makhambetov (1), Azat Shpekov (1)

1. *Vascular and Functional neurosurgery, National Center for neurosurgery, Astana, Kazakhstan*

Introduction: Parkinson disease (PD) is chronic progressive degenerative disease of the central nervous system with prevalence 72 to 258,8 for 100 thousand people. We expect up to 20000 PD patients in Kazakhstan. DBS surgery program in Kazakhstan started in 2013.

Methods: 23 PD patients were operated in the National center for neurosurgery in period 2013-2014. We used international selection criteria. We stimulated subthalamic nucleus in 22 cases and globus pallidus interna in 1 case. There were 11 males and 12 females. The average age of the patients was 51 years. The average duration of disease was 10 years. Severe fluctuations and dyskinesias were in 75% of cases. We implanted DBS therapy Aactiva PC system from Medtronic (USA), which consisted from two leads, extension cables and IPG.

Results: Improvement of motor functions was found in 80% of cases. Postural instability, gait problems and autonomic symptoms regressed less. We decreased the dosage of dopaminergic drugs up to 30% and more which resulted in regression of drug-induced dyskinesia in all cases. Moreover in two cases we postponed medication completely. We had complications in 5 cases: 1 bleeding, 1 stroke, 1 infection and 2 tromboembolism (1 of them died).

Conclusion: Deep brain stimulation is effective treatment of PD and can decrease main symptoms of the disease: rigidity, tremor and bradykinesia and sometimes postural instability and gait problems. The right patient selection is a key for good results of this procedure. There are all possibilities to treat Parkinson's disease using DBS in Kazakhstan.

#29

A new neurosurgical analysis system by image processing to determine the accuracy of frameless DBS in parkinson's disease. The nexframe-stealthstation® experience.

Pedro Roldan (1), Antonio Salvador (2), Jose Dura (3), Gabriel Calatayud (3), Jose Gonzalez-Darder (1), Jose Lainez (2)

1. Neurosurgery, University Clinic Hospital. University of Valencia., Valencia, Spain

2. Neurology, University Clinic Hospital., Valencia, Spain

3. Biomedical Engineering, Technical University, Valencia, Spain

Introduction: Our experience regarding the Stealthstation Framelink® and Nexframe® frameless system accuracy in STN DBS Parkinson's disease patients, using a new image processing system or Surgical Plan Analysis report (SPAR®) that allows for determination of the accuracy of electrode position with pre and postop multislice CT image information is presented.

Methods: During the last 12 months a group of 17 patients with Parkinson's disease has been operated using the Stealthstation S7® and the frameless Nexframe® system.

A preop 3D T1W MRI was performed and 6 fiducials were screwed into patient's skull with local anesthesia prior to surgery. Then a preop multislice CT with fiducials was obtained and fusion achieved. In the OR and under local anesthesia and light sedation, with patient's head over the passive headrest, that allows slight movements, lines and BIS in place, two burr-holes were performed according to previous MRI and CT fusion and tracks planification. After positioning the Nexframe® tower, single microelectrode recordings were obtained, followed by final electrode placement according to the microrecordings that best covered the whole STN volume. Planned targets corrected by microelectrodes findings and current electrodes contact positions were measured in triorthogonal and probe's eye view, in order to assess the accuracy of the system. The indirect targeting system, after visualization of the AC-PC line in 3D T1W MRI preop images using predetermined STN Stealthstation® coordinates, was routinely used. For electrodes accuracy determination, target and entry points were planned, and postop multislice CT was routinely performed and images used to mark the contacts final electrode position. Then the distance between the planned target as corrected by microelectrode findings and the current electrodes contacts position on postop control CT was obtained. Furthermore a 3D reconstruction of the STN in most cases and the surgical intervention could be achieved using the Amira® software on a workstation so as to get an overall picture of the whole procedure. DTI images could also be injected into the system so as to visualize the tracts involved in the stimulation and recording procedures.

Results: The average number of tracks in the first vs the second side was 1.6/1.9, due to microrecordings findings as it refers to brain target changes due to pneumocephalus and time-dependent brain-shift. The mean \pm SD distance between the postop electrode and the planified target was 1.1 ± 0.8 and 1.6 ± 1.1 for the first and second side respectively. A binding in the half distal part of the final electrode, near the burr-hole, was observed, maybe due to brain movement in the immediate postop period, apart from brainshift and possible air entry into the skull. That is why the contact positioned in the assumed target was routinely the second instead of the most distal one, so as to cover the whole STN volume.

Conclusion: The accuracy of frameless is roughly similar to that of framebased systems, with no differences in clinical results in our series, and may be next generation in functional navigation, as it is already being routinely used in brain biopsies, tumor navigation-guided surgery and even radiosurgery.

#33

Lead location for subthalamic nucleus deep brain stimulation using a 3D visualization tool

Ignacio Regidor (1), Francisco Estella (2), Lidia Cabañes (3), Marta del Alamo (1), Luis Ley (4)

1. Unidad de Neurocirugía Funcional, Hospital Universitario Ramón y Cajal, Madrid, Spain

2. Departamento de Arquitectura y Tecnología de los Computadores, Bioingeniería, Universidad de Granada, Granada, Spain

3. Neurofisiología Clínica, Hospital Universitario Ramón y Cajal, Madrid, Spain

4. Servicio de Neurocirugía, Hospital Universitario Ramón y Cajal, Madrid, Spain

Objective: This paper presents a comparison of three visualization tools used to measure the location of the implanted deep brain stimulation (DBS) leads relative to the subthalamic nucleus (STN) target.

Methods: A total of 10 DBS leads implanted in five Parkinson's disease (PD) patients with different DBS systems were studied. Implanted leads were located in a post-op CT. Three different techniques were used to locate the target; post-op CT was fused with either (1) pre-op T2 MRI imaging, (2) the Schaltenbrand atlas (Stealth Station™, Medtronic), or (3) a 3D visualization tool using the Morel atlas (Guide™, Boston Scientific).

The lead location in relation to the target was measured in millimeters with the three techniques (anterior-posterior and medial-lateral lead-target distance). The 'gold standard' for validation was the first method, direct location of the STN target using the MRI T2 images (1). The actual lead and target were located in axial slices of the image; axial-oriented planes were chosen for two main reasons: the inconsistency of 3D reconstruction for atlases such as Schaltenbrand; the normalized technique to find the STN in the MRI T2 images (1) uses axial planes to find the red nucleus and then the STN.

Results: Of the ten leads studied, 80% using the Schaltenbrand atlas (2) and the 3D visualization tool (3) showed the same relative target-lead position as the 'gold standard' (direct visualization of target with T2 MRI) (1). Two leads showed a divergence in the lead-target distance using the atlas (2) and the 3D visualization tool (3) compared with the normalized technique of target location and lead position (1), with equal deviation using the atlas (2) and the 3D visualization tool (3). Within the eight leads where the relative location measured with the three systems was equal, the lead-target distance differed: three leads were implanted directly in the desired target (lead-target distance 0 mm); five leads were implanted with a deviation from the target (lead-target distance [0.7-3.1] mm – the same distance deviation was observed when the actual T2 (1) and lead position image was compared with the atlas (2) and 3D visualization tool (3).

In the 20% of cases with a lead-target distance mismatch using method (1) vs. methods (2) and (3), a clear deviation within the anatomy of the patient and the normalized atlas was shown. This location misalignment within procedures for the atlas-related positioning and the 3D visualization tool was linearly related to the deviation in the patient-specific anatomy compared to the standardized anatomical atlas. For these 'error cases', the deviation in the position of the actual target compared with the atlas targets used in the two groups to validate was the same as the deviation of the lead location compared to the reality of the lead position.

Conclusion: These results confirm that tools such as the 3D visualization system could be a reliable tool to facilitate programming in PD patients implanted with a DBS system in all cases where the patient has a standard anatomy similar to the atlas – leading to a decrease in the programming time needed with the patient, as well as optimization of programming options. For patients with a clear deviation within their anatomy and the standard atlas, the best approach would be to take that deviation into account when using such tools for programming.

Raw data will be presented, such as deviation millimeter measurements, error values, target location drawings and correspondence with clinical outcomes. This method will allow us to validate systems such as the 3D visualization tool (Guide™, Boston Scientific) and enable its use as a trusted tool to obtain optimal programming options.

#38

Intraoperative CT scan utility in evaluation of DBS lead implantation

Domenico Servello (1), Claudia Menghetti (1), Edvin Zekaj (1), Giovannie Broggi (1), Mauro Porta (1)
1. Neurosurgery, IRRCS GALEAZZI Milan, Italy

Introduction: DBS has a worldwide spread for movement disorders, such as Parkinson Disease, Dystonia and tremor. Efficacy of DBS depends on correct lead positioning. Post-operative radiological evaluation is done with brain CT scan and/or brain MRI.

The objective is the evaluation utility of intraoperative CT scan for lead positioning in DBS.

Methods: We have evaluated retrospectively 160 patients who underwent DBS from January 2009 to October 2013. Diseases treated with DBS were: Parkinson's disease, PSP, tremor, Dystonia, Tourette, OCD, Depression and Huntington disease. Pre-operatively all patients underwent brain MRI and brain CT scan with stereotactic frame positioned. Lead position was confirmed intraoperatively with CT scan (O-Arm, Medtronic). CT scan images were subsequently transferred to Stealth Station Medtronic and merged with pre-operative planning. On the first or second day after implantation we performed a brain MRI to confirm the correct position of the lead.

Results: The most diffused evaluation of lead position in DBS is with post-operative brain CT scan or brain MRI. One of the major limits of post-operative radiological evaluation is that the patient must leave the operating room. Intraoperative CT scan reduces time of control and in cases of lead misplacement the reimplant is performed immediately.

Conclusion: Intraoperative CT-scan is fast, safe and useful tool in evaluation of lead implantation site. It also reduces the patient discomfort derived from the transfer of the patient in the radiological department. We also think that intraoperative CT cannot substitute post-operative MRI.

#49

Deep brain stimulation in movement disorder. Experience in three years using 3 mm length active tip lead and high frequency constant current stimulation.

Muñoz Jorge (1), Alvarez Ramiro (2), Blanco Alberto (1), Cladellas Josep Maria (3), Tardaguila Manel (1), Rimbau Jordi (1)

1. Neurosurgery, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain

2. Neurology, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain

3. Neurosurgery, Hoapital Universitari Germans Trias i Pujol, Barcelona, Spain

Introduction/Methods: 43 patients, aged between 49 and 70 were evaluated before and after undergoing surgery, using internationally accepted scales. We performed stereotactic technique, together with indirect target planning using CT and MR fused studies and deep brain microrecordings. Both leads and IPG are implanted on the same day. 24 hours after surgery constant current stimulation starts.

Results: 86 leads were implanted. We performed microrecordings along 3 simultaneous trajectories in each hemisphere. Average surgical time was 4,7 hours and hospital stay was 4,9 days. Most distal lead pole is positioned 0,5 mm cranial to desired area's end. In 2 cases extensions were replaced and 1 patient suffered from lead disfunction. We observed significant improvement in UPDRS part 3 not only in OFF stage but also ON-Stage related dyskinesias reduction. We also observed in L-Dopa equivalent dose reduction in Parkinson's disease patients.

Conclusion: Subthalamic DBS using tetrapolar active tip lead continue to be a safe and effective treatment in Parkinson's disease achieving motor improvement without undesired side effects. Meticulous positioning of stereotactic frame and paying attention to entrance angulation related to AC-PC plane is essential in order to achieve high accuracy method.

#56

DTI-tractography for stereotactic planning of deep brain stimulation for tremor

Donatus Cyron (1), Fernando Garcia (2), Jesse Ross-Jones (2), Vitor Vieira (3), Fabian Meisel (4), Uwe Spetzger (1)

1. Neurosurgery, Städtisches Klinikum, Karlsruhe, Germany

2. Institut für Prozessmesstechnik und innovative Energiesysteme, Hochschule Mannheim, Mannheim, Germany

3. Precisis AG, Heidelberg, Germany

4. Neurology, Städtisches Klinikum, Karlsruhe, Germany

Introduction: Evidence accumulates that targets in white matter tracts provide superior results compared to traditional targets within basal nuclei for treatment of tremor in deep brain stimulation. Stereotactic targeting of these structures in the white matter, however, so far relies on ACPC-coordinates or indirect targeting with delineation of adjacent nuclei in T2-weight MRI. Our experience with integration of tractography for direct visualisation of white matter connections for targeting in DBS is described.

Methods: Seven patients (3 Parkinson's disease, 3 essential tremor, 1 Holmes tremor) were treated with deep brain stimulation in the posterior subthalamic area. Tractography images based on diffusion tensor imaging (DTI) were coregistered with T2-weight images and high resolution T1-images on a commercially available planning system. Targets were defined integrating tractography, T2-weight images and ACPC-related coordinates derived from the literature.

Results: Excellent tremor control was achieved with little side effects and low voltages compared to DBS in the v.i.m. Long fiber connections arising in the dentate nucleus projecting to the thalamus could be detected consistently by tractography following the expected (anatomic) course of the cerebellothalamic tract (drt=dentato-rubro-thalamic tract). Limitations were motion artefacts and distortions of DWI-images in some cases. Mirroring of fibers proved difficult to overcome with tractography based on diffusion tensor imaging. In additional experiments using constrained spherical deconvolution (CSD) more crossing fibers could be detected.

Conclusion: Subthalamic stimulation appears to be superior to v.i.m stimulation. Tractography was helpful in defining target points and refining the angle of trajectories. In some cases technical limitations notably distortions of DWI-images impeded planning based on tractography. With further refinements (CSD) problems like mirroring may be solved. Long imaging times and the at present low resolution should be addressed with improved imaging protocols and faster MR-scanners. Tractography is felt to be a promising tool for stereotactic surgery if used with caution.

#63

Technical reasons for differences in intraoperative findings in semi - macrostimulation and postoperative neurological state in respect to dysarthria or other side effects?

Wilhelm Eisner (1), Florian Sohm (1), Thomas Fiegele (1)

1. Neurosurgical, Medical University Innsbruck, Austria, Innsbruck, Austria

Introduction: Deep brain stimulation in Parkinson's Disease, essential tremor and various forms of dystonia is well established and in its effectiveness proven. To identify side effects like dysarthria or motor symptoms as early as possible surgery is generally performed under local anesthesia in combination with intraoperative stimulation. But despite of that, patients seldomly show side effects postoperatively.

Methods: We examined the recording microelectrodes and stimulating semi-macro-electrodes by magnifying glasses during surgery.

Results: We never discovered a problem in the tungsten electrodes for micro-recording but some of the stimulation probes exhibited an inappropriate isolation. The insulation was still covering the tip of the probe resulting in no stimulation side effects during surgery. It was leading the surgeon and the neurophysiologist to the wrong estimation that the electrode placement will be perfect. This was proven wrong in postoperative side effects.

Conclusion: Surgeons have to be aware that mal-production of electrodes may occur being not detectable by threshold measurement of the electrodes because of bridging liquids in the surgical site. The surgeon has to check every electrode before inserting into the guide tubes especially when electrodes are delivered in sterile trays by manufacturers.

#65

A Possible Pathogenic Mechanism of Hemifacial Spasm: Hemodynamic Effects caused by Venous Sinus

Moonyoung Chung (1), Ryoong Huh (1), Inbo Han (2), Sang-Sup Chung (2)

1. Neurosurgery, Incheon St. Mary's Hospital, The Catholic University of Korea, Incheon, South Korea

2. Neurosurgery, Bundang CHA Hospital, Seongnam, South Korea

Objective: To verify our hypothesis that a hemifacial spasm occurs on the side of smaller posterior fossa venous sinus.

Methods: Retrospectively, we reviewed medical records of consecutive patients undergoing microvascular decompression to treat hemifacial spasm (HFS) from 2003 to 2014. For determining dominance of the venous sinus, dominance index was calculated. Areas of both sigmoid sinuses were measured and dominant transverse sinus receiving larger volume of venous blood from superior sagittal sinus were determined.

Results: Number, mean age and disease duration of the enrolled patients was 370, 53.8(± 10.1) and 4.64(± 6.1). Dominant index was not significantly different between right and left HFS. After grouping by offending artery, dominant index of PICA offender group were meaningfully different ($P=.019$) between right ($0.096 \pm .326$) and left ($.231 \pm .317$) HFS. Interestingly, the major offender of right and left HFS was different (AICA and PICA, respectively), and mean age of right and left HFS was different too (51.3 ± 10.6 and 54.2 ± 10.6 , respectively).

Conclusion: The side of HFS by PICA offender is mutually related with the side of non-dominant SS. The pressure difference between dominant and non-dominant SS will makes the arterial flow difference between both VA, which could be explained by Ohm's law. That might be a possible explanation for other unexpected findings: the major offender in right HFS is AICA, while that in left is PICA; mean age of patients with HFS by PICA offender is higher than by AICA.

#66

Case report: A patient with fixed dystonia successfully treated by pallidal deep brain stimulation

Fusako Yokochi (1), Makoto Taniguchi (2), Ryouichi Okiyama (1), Takashi Kawasaki (2), Kouichi Hamada (2)

1. Neurology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan

2. Neurosurgery, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan

Introduction: Fixed dystonia is an intractable disease. Many patients with fixed dystonia had dystonia following an injury and suffered from a psychiatric disease. Here, we report the case of a patient with fixed generalized dystonia, who was successfully treated by pallidal deep brain stimulation (DBS).

Case description: The patient was a 20-year-old female. She first noted extreme sleepiness during her school life when she was 15 years old. She had stiffness of her lower extremities and clumsiness in both hands. Four months, she was unable to walk by herself and finally she required the use of a wheelchair. The stiffness of her upper extremities also worsened. She was able to grasp objects, but unable to release them. She had stiffness of facial muscles with difficulty in speech and chewing. The stiffness of muscles in the face and extremities were painful. She had no history of injury or operation. Neither medications nor botulinum toxin therapy improved her symptoms. She had respiratory and swallowing difficulties due to painful muscle stiffness. Respiratory support with tracheal intubation and a respirator was necessary. She was treated by pallidal DBS. After pallidal DBS, the stiffness of her extremities and face gradually improved. Six months later, she was able to return to school and graduated high school. Her symptoms fluctuated during the following three years and psychogenic dystonia was suspected. Three years later, the stiffness of her extremities relapsed owing to the implantable pulse generator (IPG) battery running out of power. A new Activa IPG was implanted. At present, her symptoms have improved and she has started studying at a technical school.

Results: (1) Genetic examinations showed that she was negative for DYT1 and DYT12. Immunochemical analysis showed that she was negative for the anti-GAD autoantibody. (2) Brain MR images showed a slightly progressive atrophy of the frontal lobe. Brain blood flow analysis by SPECT showed a low perfusion level in the frontal area. (3) Psychiatric examinations did not show mood disorder or somatization disorder. The examination of cognitive function showed severe attention disorder and memory disturbance. (4) She was able to walk or stand with her eyes open, but not with her eyes closed. Severe position sense and deep sensation dysfunctions were observed.

Conclusion: Fixed generalized dystonia with position sense dysfunction and memory disturbance was observed. Fixed dystonia was treated by bilateral pallidal DBS. It took time to improve fixed dystonia with stiffness and pain. But however, the dysfunction of position sense and memory disturbance did not improve. The findings of MRI and SPECT indicate a degenerative disease, but its exact diagnosis is still undetermined.

#69

Cerebrospinal fluid content of neurostimulator pocket – complication of deep brain stimulation in movement disorders – a case report.

Dusan Urgosik (1), Robert Jech (2), Stefan Raev (3), Petr Dusek (2), Daniela Stastna (3), Filip Ruzicka (2), Roman Liscak (1), Evzen Ruzicka (2)

1. Stereotactic and radiation neurosurgery, Na Homolce Hospital, Prague, CzechRepublic

2. Department of Neurology and Center of Clinical Neuroscience, Charles University, Prague, CzechRepublic

3. Department of neurosurgery, Na Homolce Hospital, Prague, CzechRepublic

Introduction: Deep brain stimulation (DBS) is a stereotactic procedure with minimal intra-operative risk. However, the implantation of foreign material into the patient's body is associated with a higher frequency of post-operative complications. We present an unusual complication.

Methods: A 54-year-old patient with Parkinson's disease underwent bilateral implantation of DBS to the nucleus subthalamicus (STN). A Medtronic system with quadrupole electrodes (QE) type 3389 and Kinetra dual generator (IPG) were implanted. QE were inserted from the frontal burr holes with a diameter of 14 mm after the cross incision the dura and after micro-recording with tungsten electrodes. Burr holes were filled with tissue adhesive (Beriplast) and QE were fixed by the Stimloc system to the skull. QE were connected to the connecting extension and by tunneling procedure joined with the IPG that was placed in a subcutaneous pocket (SP) on the left side of the chest in the subclavicular region.

Results: The 4th day after implantation of the IPG significant fluctuations appeared in the SP and serous fluid oozed between stitches. We loosened the stitches and dropped the contents of SP. We took a sample for bacteriological examination and then cleaning and resuturing of the wound followed. Patient was without total and local manifestations of infection, laboratory inflammatory markers were negative. SP refilled again for two days. We punctured the SP and aspirated 40 ml of serous fluid. In the following four days, we performed two other punctures of the SP and aspirations of 60 and 80 ml of fluid of xanthochromic appearance. Bacteriological cultures were repeatedly negative. As there was an absence of inflammatory symptoms the fluid sample was sent for testing (Beta-trace protein) for the presence of cerebrospinal fluid (CSF). The result was positive and confirmed the presence of CSF in the SP. Subsequently, the 8th day after DBS, lumbar drainage (LD) was introduced with drainage up to 160 ml of CSF per 24 h. Chest compression over the SP was applied as well. After 24 h the SP was without filling. LD and chest compression were left a total of 8 days. New filling of the SP did not appear after the termination of the LD.

Conclusion: The surprising result confirming the presence of cerebrospinal fluid in the SP is a practical lesson in similar cases where bacteriological examination of the content the SP is negative and there are not laboratory or clinical signs of infection. Early implementation of LD can avoid repeated puncture of a SP and secondary introduction of infection into the SP with subsequent colonization of the DBS system.

#80

Holmes tremor in a patient with progressive multifocal leukoencephalopathy .

Vimal Raj Nitish Gunness (1), Georges Dooms (1), Bernd Wauschkuhn (2), Wolfgang Feiden (3), frank hertel (1), Nico Diederich (4)

1. Neurosurgery, Centre hospitalier du luxembourg, Luxembourg city, Luxembourg

2. Departement of Neurology, Hospital of Ettelbruck, Luxembourg, Luxembourg

3. Histopathology, Histopathological center Trier, trier, Germany

4. Departement of Neurology, Center Hospital, Luxembourg, Luxembourg

Introduction: Progressive multifocal leukoencephalopathy (PML) is a rare, sometimes fatal viral disease in patients with primary or secondary immunosuppression.

Case Description: 57- year old immunocompetent woman with intractable Holmes tremor and elongated unique brainstem lesion. The CSF screening for JC virus was negative and the diagnosis was established by brain biopsy. The course was rapidly fatal.

Results and conclusion: This atypical presentation of PML in an immunocompetent patient illustrates that diagnosis can be missed without brain biopsy.

#91

A method for electric field simulations and acceleration measurements for intraoperative test stimulation

Simone Hemm-Ode (1), Daniela Pison (1), Fabiola Alonso (2), Ashesh Shah (1), Jérôme Coste (3), Jean-Jacques Lemaire (3), Erik Schkommodau (1), Karin Wårdell (4)

1. *Institute for medical and analytical technologies, University of Applied Sciences and Arts Northwestern Switzerland, Muttenz, Switzerland*

2. *Linköping University, Department of Biomedical Engineering, Linköping, Sweden*

3. *Image-Guided Clinical Neurosciences and Connectomics (EA 7282, IGCNC), Université d'Auvergne, Clermont-Ferrand, France*

4. *Department of Biomedical Engineering, Linköping University, Linköping, Sweden*

Introduction: Despite an increasing use of deep brain stimulation (DBS), the fundamental mechanisms underlying therapeutic and adverse effects and the optimal stimulation site remain largely unknown. Computer simulations of electric entities such as electric field or current density are increasingly used to try to identify the stimulated volume around implanted DBS electrodes. So far no group has considered simulations for intraoperatively obtained test stimulation data. The aim of the present paper is to propose a methodology allowing an optimal exploitation of test stimulation data and of the clinical outcome quantitatively assessed by acceleration measurements. By performing patient-specific electric field simulations for stimulation amplitudes at different anatomical positions we aim at getting supplementary data about implicated structures and the mechanism of action of DBS. In order to illustrate technical and clinical feasibility, the presented methodology has been applied to one patient.

Methods: One patient with essential tremor presenting tremor and bilaterally implanted in the ventro-intermediate nucleus (Vim) has been included in the present study. Vim and its anatomic neighbors were preoperatively manually outlined using the iPlan software (Brainlab, Feldkirchen, Germany) according to spontaneous MRI contrasts. The identified structures were exported via a specifically designed interface based on VVLink (Brainlab, Feldkirchen, Germany) and VTK (VTK 5.2.0, Kitware Inc. Clifton Park USA). During the intervention, intraoperative test stimulations were performed in 8 to 9 positions per trajectory and on four trajectories (two per hemisphere). Tremor was recorded using a 3-axis accelerometer at each stimulation position just before the start of test stimulation (=baseline) and during the tests. Changes in tremor were expressed as percentage improvement compared to baseline. For each stimulation position, two stimulation amplitudes were chosen for electric field simulations, one with no or low clinical improvement and one with high improvement. A finite element method was applied to calculate the electric field distribution. Conductivity values were deducted from the patient's T1 weighted MRI. An isofieldlevel of 0.2V/mm was chosen and the points of the isosurface were exported. Isosurface, extracted anatomical structures and trajectories were visualized together. The percentage and the number of appearance of each structure inside the isosurface were calculated and respectively noted. The number of appearance identified with the simulation based approach and from the classical approach where only the anatomical position of the center of the measurement electrode is considered, were compared. A correlation analysis was performed between the clinical change and the percentage of the structure covered by the electric field, taking into account the data of all positions.

Results: 69 electric field simulations were performed in total for the four trajectories. Structures identified at least once inside the isosurface of the electric field were the intermediolateral (InL), the dorsolateral (DL), the ventrooral (VO), the Vim, the ventrocaudal medial (VCM) and the center median (CM) nucleus. When comparing the numbers of appearance of each structure between the simulation based and the classical approach, the VO and VCM appeared more often and the DL only appeared with the simulation based approach. The highest improvement was obtained when VO, VCM and CM were present inside the stimulated volume. The correlation of the percentage improvement with the percentage of structure included in the isosurface showed that in some structures (VCM, CM, DL, VO) the clinical improvement varied a lot without a significant change in the percentage of structure volume included. In the InL and Vim an increase of structure parts might correlate with an increase in clinical improvement.

Conclusion: A workflow and methodology making possible electric field simulations on manually outlined anatomical structures could be established. This new concept will allow the analysis of a high amount of intraoperative data obtained in a clinical study which might help to elucidate the mechanism of action of DBS. First results seem to confirm published data hypothesizing that the stimulation of other structures than the Vim might be responsible as well for good clinical effects. But the analysis of more data is necessary to draw any final conclusion.

#92

Intraoperative tissue resistance measurement using DBS electrode for movement disorders

Etienne Pralong (1), Laura Cif (1), Xavier Vasques (2), Marc Levivier (1), Jocelyne Bloch (1)

1. Clinical Neurosciences, CHUV, Lausanne-CHUV, Switzerland

2. Blue Brain Project, EPFL, Lausanne, Switzerland

Introduction: DBS addressed to several targets is a validated therapy for treating movement disorders. However, therapeutical response is heterogeneous and furthermore, occurs for different intensities of DBS settings. Computational models can provide insight into the mechanisms of action of DBS. However, the models need sufficient detail and sharpness to accurately predict potential distribution. Tissue resistance is one of the major factors influencing potential distribution during DBS and little is known about its variability in vivo in humans and specifically for DBS targets, since the majority of the impedance properties are measured in vitro, through near-physiological saline electrolyte and in vivo, in animals. We directly measured tissue resistance between electrode contacts during DBS procedures addressed to the STN or VIM in Parkinson's disease patients with the aim to identify a physiological measurement supporting the highly variable levels for DBS settings applied to obtain clinical response.

Methods: During DBS surgical procedures, constant current squared pulses (200 μ s duration, 0.5 Hz, monophasic) were applied between Medtronic® 3387 or 3389 electrode contacts, using the low stimulation output of an Eclipse® intra operative monitoring system at 1, 1.5 and 2 mA of intensity. The Medtronic® 3387/3389 DBS electrode has four contacts, named from 0 to 3 (ventral to dorsal). Voltage deflections were visualized and measured in parallel on an oscilloscope. Resistance is expressed as $R=U/I$, regardless tissue/electrode impedance. For between-electrode measurements, stimulations were applied between contacts 0-0, 1-1, 2-2, 3-3 and for within electrode measurements, between contacts 0-1, 0-2, 0-3. For within electrode data, resistance between contacts 1-2 was calculated as the difference of the resistance between contacts 0-2 and 0-1. In the same way resistance between contacts 2-3 was computed as the difference between 0-3 and 0-2.

Results: For all electrode contacts, resistance did not vary with applied current (1, 1.5 and 2 mA) therefore total resistance for a contact pair was computed as the average of the three measures. Between-electrodes, measurements for resistance ranged from 1.95 to 2.45 kOhm (average = 2.14 ± 0.14 , $n=12$). Resistance did not correlate with contact distance as measured on intraoperative O-Arm acquisition or on contact impedance. Within-electrode resistance ranged from 1.56 to 2.42 kOhm (average = 1.96 ± 0.21 , $n=18$). Resistance correlated with contact distances (i.e. bigger for 0-r compared to 0-1). Preliminary result suggests that for STN electrodes, resistance between contacts 1 and 2 (226 Ohm) was bigger than resistance between contacts 2 and 3, more dorsally located (42 Ohm).

Conclusion: This preliminary results suggest in one hand that resistance increases with inter-contact distance, when tested within the same electrode. On the other hand, resistance variations between contacts of two distant electrodes implanted within the STN nucleus bilaterally is not correlated to the inter-contact distance. Voltage deflection measured during constant current stimulation would rather be a complex response, depending on the resistance, capacitance and inductance properties of the brain tissue.

#96

Peri-electrode oedema after DBS implantation: case report.

Alberto Bona (1), Andrea Trezza (1), Clarissa Cavandoli (1), Manuela Pilleri (2), Angelo Antonini (3), Erik Sganzerla (1), Andrea Landi (1)

1. Neurosurgery, San Gerardo Hospital, Monza, Italy

2. Neurology, IRCCS San Camillo, Venezia, Italy

3. Neurology, IRCCS San Camillo, Venice, Italy

Submitter: Mr Landi Andrea (IT)

Introduction: Peri-electrode oedema after DBS implantation, not due to infection, is infrequently reported; usually it is asymptomatic and may be a potential CT scan finding in the first days after surgery. Causes of oedema are considered to be: direct brain injury, a-specific anaphylaxis or specific anaphylaxis for prosthetic materials. Leads removal versus anti-oedema therapy are suggested from different Authors. In this work we present a case of a symptomatic post-operative oedema occurred around deep brain stimulation leads in a patient treated in our Centre.

Methods/results: Patient was a 49 years old caucasian male, affected by juvenile Parkinson's disease. He was selected for DBS according to London Brain Bank protocol. After CAPSIT evaluation preop off UPDRS was 53; L-Dopa response (spot 150 mgs) was greater than 40%; no cognitive nor psychiatric derangements were detected; preop MRi was normal. He was submitted to bilateral subthalamic DBS; surgery occurred without hitches; postop "lesional" effect was very clear on motor items (UPDRS off med 26). The patient was discharged 4 days after surgery without worries. Peri-operative antibiotic prophylaxis was administered, pre and post operative blood tests were normal.

Seven days after surgery, the patient presented with a progressive state of apathetic, reduced motor activity and less fluent speech, with somewhat errors of denomination and paraphasias; no focal neurological deficits were present. Brain CT scan showed bilateral hypodense areas surrounding both DBS electrodes, without contrast enhancement: this imaging was interpreted as oedema. Patient was afebrile and did not complain with head ache or systemic signs. Cerebrospinal fluid (CSF) analysis and systemic blood tests for infections were negative; CSF oligoclonal-band analysis was negative too. EEG did not show anomalies. Hypersensitivity skin test (patch test) was performed using fragments from a DBS lead, to test the patient's reactivity to iridium, platinum and polyurethane; after 48-72 hours probable hypersensitivity reaction to metals (iridium and platinum) was found.

For the striking effects of DBS on motility and after the explicit willingness of the patient, we decided not to remove the leads; the patient was treated with high-dose steroids for three weeks; progressive resolution of the clinical status was achieved after 2 months; serial CT scan showed the decrease of the hypodense areas till their full vanishing after 4 weeks.

Conclusion: Peri-electrode oedema may occur occasionally after DBS; maybe it is underestimated and it should be considered in case of troublesome postoperative follow-up. After our experience, we suggest that, if clinical derangement is not so heavy, maintenance of the leads may be considered and medical therapy may obtain resolution of the clinical picture.

#98

Comparison between constant voltage and constant current stimulation in DBS for Parkinson's disease and Primary generalized dystonia.

Clarissa Cavandoli (1), Manuela Pilleri (2), Maria Chiara Sensi (3), Alberto Bona (1), Andrea Trezza (1), F. Preda (3), Angelo Antonini (4), Erik Sganzerla (1), Michele L. Cavallo (5), Andrea Landi (1)

1. Neurosurgery, San Gerardo Hospital, Monza, Italy

2. Neurology, IRCCS San Camillo, Venezia, Italy

3. Neurology, University Hospital, Ferrara, Italy

4. Neurology, IRCCS San Camillo, Venice, Italy

5. Neurosurgery, University Hospital, Ferrara, Italy

Introduction: Traditional DBS technology relies on voltage-controlled (CV) stimulation; however, recently, new current-controlled (CC) devices have been developed. These new stimulators deliver constant current to the brain tissue, irrespective of impedance changes that occur around the electrode. Some recent studies showed the longitudinal impedance variability in patients with chronically implanted DBS devices and the significant improvement in de-novo patients treated with constant-current DBS, but up to now, no data exist about the clinical modification related to the switch from chronic CV to CC stimulation, after a battery replacement. The aim of this data collection is to report a multicenter experience in the replacements from constant voltage to constant current DBS devices from a safety and efficacy point of view.

Methods: 18 patients undergoing IPG's replacements from constant voltage to constant current devices were included in this data collection. All replacements were performed by the same neurosurgeons in two Italian Centers (Arcispedale Santa'Anna – Ferrara and Azienda Ospedaliera San Gerardo – Monza). After replacements, all IPGs were switched on with the same contacts setting, pulse width and frequency used in the CV mode. The correspondence between amplitude in CV and CC was set on the base of the impedances checked in the CC devices. All programming sections were performed by the neurologists who have followed patients since the first implant. For each patient we collected:

- Number of replacements occurred, both with CV and CC devices
- Motor scores before the implant and after 3 months from the implant (UPDRS III in PD patients and BFM in DYT patients)
- Mean battery duration between each replacement
- Number of programming sections necessary to reach the same pre-replacement clinical outcomes
- Information about the programming settings and impedances of IPGs before and after the replacement
- Physician's and patient's feedback about the clinical results obtained after the replacement
- Patient's feedback about the recharging procedure
- Adverse events and side effects.

Results: 12 patients were affected by Parkinson's disease (PD) and 6 from primary generalized dystonia (DYT). CV to CC replacement was the first substitution for 3 patients (17%), while 15 patients (83%) already underwent to other replacements before the substitution from CV to CC. The mean duration of IPG's battery in all patients is 4.1 ± 1.1 years (4.5 ± 0.7 yrs in PD patients and 3.4 ± 1.5 yrs in DYT patients). The number of the reprogramming sections necessary to reach the same clinical outcomes was 1.9 ± 1 (2.1 ± 1.1 in PD and 1.5 ± 0.8 in DYT) for CV-CC replacements, and 2.1 ± 1.4 (2.5 ± 1.6 in PD and 1.3 ± 0.5 in DYT) for CV-CV replacements; no significant difference. In the 12 PD patients, UPDRS III mean score was 35.5 ± 12.1 before the replacement and 35.9 ± 13.1 after the procedure, in both cases in ON-ON condition according to CAPSIT. No significant differences in the motor score after the change in CC mode ($p = 0.854$) was recorded. In the 6 DYT patients, the BFM mean score was 25.3 ± 5 before the replacement and 23.1 ± 12.8 after the substitution, with no significant differences between the two stimulation modes ($p = 1.854$). Moreover, after 6 months 100% of patients and physicians will choose again a CC replacement. In 5 patients the IPG was replaced with a CC-rechargeable device. After a technical training, the recharging procedure was comfortable or acceptable for all of them.

Two adverse events occurred: a case of full discharge of the CC stimulator due to an insufficient training to the patient after the implant and an edema of the IPG pocket two days after the implant with spontaneous resolution.

Conclusion: According to the results of this preliminary study, the replacement from a CV to a CC stimulator seems to be a safe and efficacious procedure, without significant clinical differences between the two stimulation's modalities. CC devices seem to guarantee a stability of symptom control in patients with a long history of CV chronic stimulation. Moreover CC IPGs, could theoretically deliver a stable therapy not influenced by the physiological impedance's changes.

#99

Chronic intraventricular baclofen infusion in patients with secondary dystonia

Andrey Dekopov (1), Aleksey Tomsy (1), Vladimir Shabalov (1)
1. Functional Neurosurgery, Burdenko Neurosurgical Institute, Moscow, Russia

Introduction: Secondary dystonia is caused by different diseases of CNS. Conservative therapy and DBS have low clinical effect. We present our experience in treatment of secondary dystonia by intraventricular baclofen infusion.

Methods: 2 patients with cerebral palsy and post hypoxic condition have been operated. The weight of dystonia before the operation estimated on BFM scale was $63,5 \pm 12,02$ points. In the first case (wide ventricles) we have implanted the catheter under endoscope control, in the second case (narrow ventricles) we have implanted the catheter stereotactically with ventriculographical control. The catheter have been placed in back region of third ventricle near the aqueducts foramen. The pump have been implanted in the left subcostal region.

Results: We have obtained the clinical effect when the Baclofen daily dose has reached 100 mg/day. We have revealed significant decrease of dystonia in face, neck and extremities. The sedation effect was more meaningful compare with intrathecal infusion, but it was regressed during several days. The weight of dystonia 1 week after the operation was $33,5 \pm 2,12$ points. The clinical effect was stable in follow-up (12 months), the dose of intraventricular infusion has been increased until 130 mg/day.

Conclusion: Chronic intraventricular baclofen infusion is an effective method for treatment of movement disorders in secondary dystonia. The effective daily dose of intravenricular infusion is low than intrathecal daily dose infusion in similar patients.

#104

Simultaneous bilateral MER-guided Stereotactic implantation of DBS electrodes

Erich Talamoni Fonoff (1), William Omar Contreras Lopez (2), Rachel Martinez (3), Jairo Angelos (4), Jessie Navarro (5), Angelo Azevedo (6), Manoel Jacobsen Teixeira (7)

1. *Functional and Stereotactic Neurosurgery, University of Sao Paulo, Sao Paulo, Brazil*

2. *Functional and Stereotactic Department, University of Sao Paulo, Sao Paulo, Brazil*

3. *Functional and Stereotactic Department, University of Sao Paulo Medical School, Sao Paulo, Brazil*

4. *Functional and Stereotactic Department, University of Sao Paulo School of Medicine, Sao Paulo, Brazil*

5. *Physiology, Functional Neurosurgery, University of Sao Paulo, Sao Paulo, Brazil*

6. *Functional and Stereotactic Neurosurgery, Sao Paulo School of Medicine, Sao Paulo, Brazil*

7. *Neurosurgery, University of Sao paulo, Sao Paulo, Brazil*

Introduction: Bilateral DBS has become one of the most important neurosurgical techniques for the treatment of various movement disorders and neuropsychiatric diseases. In recent years, many efforts have been made in order to improve safety, accuracy and comfort for the patient treated by DBS. A cardinal fact is that currently the surgical step-by-step procedure involves two unilateral sequential hemispherical implants what increases surgical time and also CSF leak increasing the risk of brain shifting. In this case series we performed bilateral, simultaneous implant of deep brain electrodes, as a strategy to shorten surgical procedure avoiding major brain shift. The aim of this work was to demonstrate technique feasibility and advantages of performing bilateral simultaneous electrodes implant from a case series of 40 patients with Parkinson's disease (PD).

Methods: Forty adult patients average of age was 53 years; were submitted to DBS for treatment of PD. Twenty patients underwent traditional sequential bilateral DBS implantation while other 20 patients had the bilateral simultaneous approach. In the simultaneous approach, 2 half-arcs were mounted simultaneously on a Micromar® stereotactic frame allowing concurrent bilateral access. After two precoronal burr holes, up to three cannulas were inserted in two microdrives until 10 mm before target; microrecording was performed simultaneously at every 0.5-mm until target. The number of tracks used for microelectrode insertion ranged from 1 to 3 (median 1) and the macroelectrode in track eliciting the best clinical outcome was subsequently replaced by a permanent electrode (Medtronic® type 3387), followed by macrostimulation. Immediately after the procedure, the position of each permanent electrode was verified by orthogonal X-ray images. Statistical analysis (Student T test) was performed to analyze surgical time-length of traditional bilateral sequential DBS and bilateral simultaneous DBS procedure in our department with the same surgical team. Operating time for pulse generator implantation was not computed in this study.

Results: We found the simultaneous procedure to be consistently faster: 35,3% ($P < 0,00003$) when compared to our traditional sequential procedure (one side at a time). The average time in sequential DBS surgery was 224,44 minutes (SD: 20,68) and with simultaneous bilateral implantation it lowered to 144,7 minutes (SD:16,26). The procedure presented major advantages over traditional unilateral individual consecutive approach, such as: real time recorded bilateral neuronal activity, high accuracy between planning and surgery documented by better clinical outcomes most probably due to avoiding of major brain shifting.

Conclusion: Present data suggests that bilateral simultaneous implant of deep brain electrodes decreased significantly procedure time-length. It may also reduce the impact of brain shifting in bilateral procedures because the insertion of cannulas is performed right after dural opening. It may represent an attractive surgical alternative in any functional stereotactic departments.

#107

Deep brain stimulation for essential tremor in the elderly – a single center analysis

Johann Klein (1), Andreas Kupsch (2), Imke Galazky (3), Lars Buntjen (2), Hans-Jochen Heinze (3), Jürgen Voges (2)

1. Neurosurgery, University Hospital Dresden, Dresden, Germany

2. Stereotactic Neurosurgery, University Hospital Magdeburg, Magdeburg, Germany

3. Neurology, University Hospital Magdeburg, Magdeburg, Germany

Introduction: Deep brain stimulation (DBS) in the nucleus ventralis intermedius of the thalamus (VIM) is an established methodology for the treatment of essential tremor (ET). However, data on the outcome in elderly patients is sparse. We thus aimed at evaluating safety and efficacy of the procedure in patients >70 years vs. patients <70 years.

Methods: All patients stimulated in the VIM between 2007 and 2013 at our institution were included in a retrospective analysis and their medical records were reviewed. To compare the outcome, we split the patients in a group >70 years and a group <70 years at the time of surgery. Outcome parameters comprised the Fahn-Tolosa-Marin tremor rating score (FTM), Mattis Dementia Rating Scale, Frontal Assessment Battery (FAB), Quality of Life in Essential Tremor (QUEST), Beck Depression Inventory II (BDI-II), Activities of Daily Living (ADL), and adverse events.

Results: We identified 29 consecutive patients treated with bilateral VIM stimulation for ET (14 male). 14 patients were included in the younger group (mean age 59.5 ± 8.8 , range 43-68) and 15 patients in the older group (mean age 73.3 ± 2.6 , range 70-79). For 27 patients, postoperative data was available. One patient per group was lost during follow-up. Mean follow-up time was 14.9 months in the older group (range 3-80) and 18.8 months in the younger group (range 3-70). Postoperative CT excluded intracranial hemorrhage in all cases. There was no perioperative morbidity or mortality. Four patients of the younger group underwent revision surgery (two wound revisions, one electrode replacement followed by electrode removal, and one system removal followed by wound revision; all but two within six weeks of the initial surgery). None of the older patients had to be re-operated. Mean postoperative FTM score did not differ between the groups in the on-stimulation state (18.3 vs. 17.5, $p = 0.75$). Cognitive capacities were equal (FAB: 16.8 vs. 15.5, $p = 0.22$; MDRS: 136.6 vs. 134.8, $p = 0.92$). BDI-II was lower in the older group (13.4 vs. 5.6, $p = 0.02$) after equal preoperative values (16.6 vs. 17.5, $p = 0.83$). The QUEST (38.6 vs 25.5, $p = 0.11$) and ADL (22.1 vs. 21.0, $p = 0.70$) showed no significant differences.

Conclusion: VIM-DBS is safe and efficient in patients aged 70 years or older. No higher risk or lower efficacy could be identified when compared to patients <70 years. Depression might be influenced more favorably in the elderly.

#117

Downward displacement of a deep brain stimulation electrode ten years following implantation

Domenico Iacopino (1), Rosario Maugeri (1), Antonella Giugno (1), Cole Giller (2)

1. Neurosurgical unit, Department of experimental biomedicine and clinical neurosciences, University of Palermo, Palermo, Italy

2. Department of Neurosurgery, Georgia Regents University, Augusta, United States

Introduction: Despite the best efforts to ensure stereotactic precision, deep brain stimulator (DBS) electrodes can wander from their intended position after implantation. In many cases, the migration occurs before closure of the operative wound, and is likely due to an inadvertent movement of the electrode during the procedure. However, several centers have reported late migration of electrodes occurring months or years after the initial surgery. The majority of these displacements are in the upward direction, and are thought to be related to a tenuous attachment of the electrode to the skull that allows the electrode to slide as the head and neck are turned. Here we report a case downward electrode migration ten years following successful implantation in a patient affected by Parkinson's disease.

Case description: A 53 year old man with Parkinson's disease underwent to bilateral implantation of DBS electrodes connected to a subclavicular 2 channel pulse generator. Seven years later, the generator was replaced, and a CT scan confirmed the correct position of both leads. Three years later, ten years after the original implantation, the patient developed a gradual worsening affecting his right-side. A CT scan revealed the displacement of the left electrode inferiorly into the pons. These scans and those obtained immediately after the implantation were merged within a stereotactic planning workstation (Brainlab®). Changing the stimulation parameters to activate the most superior of the electrode contact (Contact 7) reestablished improvement in his motor symptoms. Although the position of the distal end of the electrode at its attachment to the wire leading to the generator had not changed between scans, the proximal tip of the electrode was located significantly more inferior within the brain. Furthermore, the size and configuration of the coiled portions of the electrode in the vicinity of the burrhole had not changed. The length of the electrode was measured from each of the CT datasets by dividing the electrode into short segments, using the workstation software to measure the length of each segment, and adding the results. At implantation, the electrode measured 27.7 cm; after 10 years, the electrode measured 30.6 cm. The leads are those provided by the manufacturer (Medtronic®) with a length of 28 cm. Because the distal end of the electrode and the configuration of the coiled segment had not changed, this data suggests that the electrode had been stretched into its new position rather than pushed there by a sliding process.

Conclusion: This data suggests that the electrode had been stretched into its new position rather than pushed. Clinicians evaluating patients with a delayed worsening should be aware of this rare event.

#118

Relief of occipital neuralgia due to parkinsonian cervical dystonia by C2 rhizotomy and C1-2 fusion

Ethan Taub (1), Peter Fuhr (2), Margareth Amort (2), Gregory F. Jost (1)

1. Neurosurgery, Basel University Hospital, Basel, Switzerland

2. Neurology, Basel University Hospital, Basel, Switzerland

Introduction: Pain is common in Parkinson's disease but only rarely has a cause that can be directly treated by surgery. We present an unusual case of this kind.

Case description: A 76-year-old man with a five-year history of akinesia-dominant Parkinson's disease presented with intractable left occipital pain of two years' duration. As part of his parkinsonian syndrome, he had cervical dystonia causing a marked head tilt to the left. Cervical CT and MRI studies (Figures 1 and 2) revealed arthrosis and bony overgrowth of the left atlantoaxial joint, with posterior displacement and compression of the C2 nerve root and ganglion.

Methods: The patient gave his informed consent to the proposed C2 rhizotomy with C1-2 fusion. At surgery, after exposure of the craniocervical junction on both sides, the left C2 root was identified and a segment of it was excised proximal to the ganglion (Figure 3). A C1-2 fusion was performed with four screws, a titanium cable, and an iliac crest bone graft (Figure 4; x-ray view, Figure 5).

Results: Immediately after surgery, the patient had the expected sensory deficit in the distribution of the left greater occipital nerve, and he was free of occipital pain. He was still free of pain and off analgesic medication at his last follow-up 8 months after surgery.

Conclusion: Pain in Parkinson's disease is not necessarily due to muscle rigidity alone. A remediable anatomical cause should be sought if the symptoms are clearly localizable to a particular nerve root, as they were in this case.

#119

GPi-DBS in dystonic patients using frameless versus frame-based stereotaxy: a single centre experience

S. D'Auria, M. Mondani, Christian Lettieri, S. Rinaldo, G. Devigili, M. Skrap, R. Eleopra

SOC di Neurologia - Azienda Ospedaliero-Universitaria "S. Maria della Misericordia" - Udine

Neurology Unit - University-Hospital - Udine

Neurosurgery Unit - University-Hospital - Udine

Neurosurgery Unit - University-Hospital - Udine

Neurology Unit - University-Hospital - Udine

Neurosurgery Unit - University-Hospital - Udine

Neurology Unit - University-Hospital - Udine

Introduction: Traditionally, deep brain stimulation (DBS) for movement disorders has been performed using frame-based stereotaxy. However, in recent years, it has also been performed using frameless stereotaxy. The comparable accuracy between frame-based and frameless image-guided approaches has already been demonstrated. In the same way the safety and clinical efficacy of the frameless technique has already been evaluated in Parkinson's disease but not in dystonia. The aim of this study was to compare the clinical outcome of GPi-DBS using a frameless technique with that of using a frame-based surgery in a homogeneous population of dystonic patients.

Methods: Thirty patients affected by primary segmental dystonia underwent GPi-DBS, 15 with frameless and 15 with frame-based stereotaxy. Surgery was performed under local anesthesia with the aid of microelectrode recording and macrostimulation with a multitrack technique. Programming was started soon after the implantation and the outcome of the patients was followed up regularly for at least 12 months by means of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). The BFMDRS scores were then compared between the two groups of patients by means of statistical analysis.

Results: After 1 year of follow-up, the patients who received frameless surgery showed no significant difference in the degree of improvement in motor and disability scores of the BFMDRS compared with the patients who received frame-based surgery. Moreover we did not find any significant difference regarding peri- and post-operative complications as well.

Conclusion: Our data indicate that frameless GPi-DBS has a similar efficacy and safety when compared with frame-based surgery in dystonic patients.

#132

A case series of dopamine agonist withdrawal syndrome following deep brain stimulation for Parkinson's disease

Lucy Partington (1), Monty A Silverdale (1,2), Gemma Mercer (3), Julian Evans (4), Christopher Kobylecki (1,2)

1. Department of Neurology, Greater Manchester Neurosciences Centre, Salford, U.K.

2. Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, U.K.

3. Department of Neuropsychology, Greater Manchester Neurosciences Centre, Salford, U.K.

4. Department of Neurosurgery, Greater Manchester Neurosciences Centre, Salford, U.K.

Introduction: Deep brain stimulation (DBS) surgery is indicated for motor complications of Parkinson's disease (PD). Our practice has been to withdraw dopamine agonist drugs following surgery. A constellation of neuropsychiatric symptoms relating to dopamine agonist withdrawal has recently been identified in patients with PD. The aim of this study was to evaluate the prevalence of dopamine agonist withdrawal syndrome (DAWS) in patients reducing their medications following DBS surgery.

Methods: We performed a retrospective case-note review of 22 patients with PD (mean age at surgery 60.2 ± 6.5 years, 9 female) who underwent DBS (21 bilateral zona incerta, 1 globus pallidus interna) surgery at Greater Manchester Neurosciences Centre between July 2011-July 2013. Dopamine agonists were reduced in 16 patients postoperatively, of whom four exhibited symptoms meeting published criteria for DAWS, including mood disturbance, apathy and insomnia. We examined pre-operative neuropsychological data in patients with and without DAWS.

Results: There were no significant differences between DAWS+ and DAWS- groups in age, total levodopa or dopamine agonist doses pre- or post-operatively, although a statistically significant greater proportion of DAWS+ patients were female ($n=3$, $p=0.03$). The rate of dopamine agonist withdrawal tended to be higher in DAWS+ patients. Symptoms were improved in three by either halting reduction or reintroducing low-dose dopamine agonist, and have persisted in one case.

Conclusion: Dopamine agonist withdrawal syndrome can occur post-DBS and may be challenging to manage. Possible strategies to mitigate the effect of DAWS would include withdrawal or reduction in agonist doses pre-operatively, or slower reductions post-operatively.

#140

Advanced age and neuropsychological deficits do not predict difficulty using a rechargeable Deep Brain Stimulation system in a typical cohort of implanted Parkinson's Disease patients

Stephen Carcieri (1), Lilly Chen (1), Lars Timmermann (2), Thomas Bruecke (3), Mohammed Maarouf (4), Michael Barbe (2), Fernando Seijo (5), Esther Suarez San Martin (6), Steven Gill (7), Alan Whone (8), Domenico Servello (9), Mauro Porta (10), Claire Haeg

1. Neuromodulation, Boston Scientific, Valencia, CA, United States

2. Neurology, University Hospital Cologne, Cologne, Germany

3. Neurology, Wilhelminenspital, Vienna, Austria

4. Neurosurgery, University Hospital Cologne, Cologne, Germany

5. Neurosurgery, Hospital Central de Asturias, Oviedo, Spain

6. Neurology, Hospital Central de Asturias, Oviedo, Spain

7. Neurosurgery, Frenchay Hospital, Bristol, United Kingdom

8. Neurology, Frenchay Hospital, Bristol, United Kingdom

9. Neurosurgery, Instituto Galeazzi IRCCS Milano, Milan, Italy

10. Neurology, Instituto Galeazzi IRCCS Milano, Milan, Italy

11. Neurosurgery, CHU de Rennes-Pontchaillou, Rennes, France

12. Neurology, CHU de Rennes-Pontchaillou, Rennes, France

13. Neurosurgery, Medical University of Vienna, Vienna, Austria

Introduction: Deep Brain Stimulation (DBS) systems are available with either rechargeable or non-rechargeable batteries. It has been previously reported that patient age is negatively correlated with patient satisfaction with rechargeable devices, and proposed that rechargeable devices are more beneficial for younger patients without signs of dementia (Timmermann et al, 2013). As part of the VANTAGE study of subthalamic DBS in patients with Parkinson's disease with a rechargeable system, we collected data on patients' success in recharging the device out to 1 year post-implant. Additionally, we analyzed the correlation between age, signs for cognitive impairment in neuropsychological testing and other patient demographics with measures of recharging success to determine whether any particular patient profile was associated with success of recharging.

Methods: Forty (40) subjects with Parkinson's Disease were implanted bilaterally in STN with Boston Scientific's rechargeable DBS system. Four measures of battery recharging were collected at 26 and 52 weeks post-implant, including the patient's overall ability to recharge successfully, battery charge level (number of bars) at the time of follow-up, patient-reported days since last charge, and patient-reported hours of stimulation usage. Patient demographics and standard PD assessments at baseline were also collected, including age and neuropsychological scores as measured by the Mattis Dementia Rating scale (MDRS). The magnitude of correlation between each recharging measure and patients' baseline demographics/PD assessments was calculated.

Results: In accordance with the inclusion criteria, patient age and neuropsychological scores were similar to the profile of PD patients implanted with DBS in previous studies (age range of 42-74 years with a mean of 60.2 ± 7.82 years; MDRS range of 130.0 to 144.0 with a mean of 140 ± 3.55) (Deuschl et al, 2006; Weaver et al, 2009). All patients reported being able to successfully recharge the device. 44.8% of patients presented with a fully charged battery (three bars) at follow-up, with 63.2% of patients reporting that it had been at least 3 or more days since their last recharging session and 63.1% of patients reporting that they had 48 or more hours usage. No correlation was found between age or cognitive status and any of the recharging measures ($R = -0.2106$ age vs number of bars, $R = -0.0705$ age vs hours of usage, $R = -0.0540$ age vs days since last charge; $R = -0.035$ MDRS vs number of bars, $R = -0.064$ MDRS vs hours of usage, $R = 0.109$ MDRS vs days since last charge). In a rank-ordering of all correlations between age and dementia rating (MDRS) and the 78 assessments collected at follow-up, the 3 recharging measures were in the bottom 20% of correlations.

Conclusion: The high recharging success rate across the entire patient sample, along with the lack of correlation between charging success and age or neuropsychological scores, indicates that age or cognitive impairment without signs of dementia may not be as predictive of suitability for a rechargeable DBS system as previously believed. Further research is needed to determine whether this is a result of improved ease of use in newer rechargeable DBS systems, reliance on caregiver, intensive teaching of patients, participation in a clinical trial, or some other difference with previous studies.

#145

Correlation analysis between quantitatively analyzed stimulation effects and anatomical position during deep brain stimulation surgery.

Ashesh Shah (1), Jerome Coste (2), Jean-Jacques Lemaire (2), Erik Schkommodau (1), Simone Hemm-Ode (1)

1. Institute for Medical and Analytical Technologies, University of Applied Sciences and Art Northwestern Switzerland, Basel, Switzerland

2. Image-Guided Clinical Neurosciences and Connectomics (EA 7282, IGCNC), Centre Hospitalier Universitaire de Clermont-Ferrand, Université d'Auvergne, Clermont-Ferrand, France

Introduction: DBS is a routinely performed surgical procedure for treatment of movement disorders like Essential Tremor (ET). However, the target selection in DBS is not fully optimized. Incomplete knowledge of the mechanisms of action being one of the reasons, we believe, suboptimal usage of information during surgery is another. We have previously demonstrated the use acceleration sensors to quantify changes in patient tremor during deep brain stimulation surgery. In this paper, we would like to analyze the correlation of the acceleration data results with the different deep brain structures. We present in this paper the result from 5 ET patients implanted in the VIM.

Methods: A 3 axis acceleration sensor was used to record and quantify changes in the patient's tremor while test stimulations were performed during DBS surgery using the method described previously. During surgery, for every test stimulation position, the maximum change in patient's tremor and the stimulation amplitude at which it was observed subjectively were noted. As the acceleration data was continuously recorded, it was possible, from offline analysis, to find stimulation amplitudes for changes in statistical features equal to those found subjectively. Additionally, the stimulation amplitudes at which acceleration data suggested maximum change in tremor were also identified for every test stimulation position. For the anatomical analysis, the surgical team carefully identified the anatomical location of the electrode and attributed one thalamic sub-structure to it. Based on this information, the change in tremor and its corresponding stimulation amplitude were grouped into respective sub-structures. For the identification of most effective anatomical sub-structures, we checked for higher reduction in tremor at lower amplitude, both for subjective evaluations and acceleration data analysis.

This method was applied to acceleration data collected from 5 Essential tremor patients under a clinical study in University Hospital in Clermont-Ferrand France. A total of 107 test stimulations were analyzed. The different sub-structures of the thalamus have been named according to the previously published nomenclature.

Results: The 107 different test stimulation positions were found to be distributed in different parts of the thalamus: Intermedio-Lateral (InL, n=20), Ventro-Oral (VO, n=16), VIM (n=37), Ventro-Caudal-Lateral (VCL, n=2), Central-Medial (CM, n=3), Ventro-Caudal-Medial (VCM, n=23) and the PreLemniscal Radiations (PLR n=6). As the number of test stimulations in the VCL, CM and PLR is low, the significance of the results is very low. For the other structures, the effective stimulation amplitudes for the same clinical effect were lower for acceleration data than the subjective ones ($p < 0.01$, $\alpha = 0.05$). On the basis of subjective evaluation data, we found that for same average effective stimulation amplitude (1.8 mA), the average reduction in tremor was higher for VCM (74%) than for VIM (55%). The results from the acceleration data were similar: The stimulation amplitude required for maximum change ($>75\%$) was on average lower in the VO (1.8 mA) and in VCM (1.9 mA) as compared to the VIM (2.5 mA) and in InL (2.5 mA).

Conclusion: The use of sensitive acceleration measurements during the surgery introduces a new approach to analyze the effectiveness of stimulation in different target structures. Our results suggest that the VCM is a better target than the VIM. This information should be considered during the planning of the exploration paths to have more contacts in the effective thalamic area. However, the current analysis does not take into considerations stimulation induced side effects. Those influence the final implant position significantly and can alter our conclusion. Also, attributing one stimulation position to just one structure considering it as a point is suboptimal. A better approach would be to simulate the stimulated volume by using electric field simulations. Along with additional analysis of the results with reference to the known mechanisms of actions of DBS they may result in increasing our understanding of DBS efficiency.

#146

Surgical Experience with Miniature Rapid-Prototype Stereotactic Frames for Deep Brain Stimulation

James McInerney (1), Namath Hussain (1), David Carr (1), Oliver Mrowczynski (1)
1. Neurosurgery, Penn State Hershey Medical Center, Hershey, United States

Introduction: DBS is a novel treatment that utilizes the three dimensional stereotactic targeting of nuclei below the cortical surface. It has been used with success for several disorders including Parkinson's Disease (PD) and Essential Tremor (ET). It requires precise targeting with a high degree of accuracy which has traditionally been achieved by using a stereotactic frame, which entails significant operating room time and cost for intraoperative imaging and planning. New customized, miniature rapid-prototype stereotactic frames called STarFix (surgical targeting fixture) have been developed that offer the advantage of moving intraoperative imaging and planning into the outpatient setting which is then followed by the generation of a custom, patient-specific skull-mounted stage. We compared the time and cost efficiency of the STarFix system to the traditional frame-based method of implantation along with clinical outcomes.

Methods: A retrospective chart review was performed analyzing procedural time and costs for placement of bilateral deep brain stimulating electrodes using the Leksell stereotactic frame-based system (Elekta Instruments, Atlanta, GA) and the STarFix platform system (FHC, Bowdoinham, ME). Secondary outcome measures were medication use, patient self-report of symptoms, and neuropsychological evaluation at 3 months. For neuropsychological evaluation, the Dementia Rating Scale (DRS) and Mini-Mental Status Exam (MMSE) were administered.

Results: Of the 157 patients implanted for PD or ET, 8.9% were placed using the Leksell frame-based technique and 91.1% were placed using a frameless technique. Average hospital length of stay (median 1 day) was similar between patients receiving frame-based or STarFix deep brain stimulator placement. Total charges for the stay were 11% greater in the group that underwent the Leksell stereotactic frame-based procedure. The operating room charges, which included the hardware costs, were 15% less in the group that underwent STarFix deep brain stimulator placement. Mean operative time for bilateral electrode implantation using the STarFix system was 206 minutes (range 116 to 457 min), which was 47% less than deep brain stimulator placement procedure performed using the Leksell frame for bilateral electrodes at a mean of 388 min (range 307 to 530 min). No patients reported increases in medication requirements. There were no significant differences in MMSE change, DRS scores, medication decrease, or symptom improvement at 3 months.

Conclusions: Electrode placement using the STarFix platform was more time and cost efficient than using the standard Leksell frame-based system. The mean operating room time was substantially reduced, reducing costs and improving the patient experience. There were no differences in cognitive outcome in patients that underwent placement using the STarFix system at three months. There was no difference in medication use, self report of symptoms, or objectively measured neurocognitive performance. We believe that appropriately selected patients can benefit from DBS implantation using the STarFix platform.

#150

Aim for the suprasternal notch:

Technical note to avoid bowstringing after deep brain stimulation

Harith Akram (1), Jonathan Hyam (2), Patricia Limousin (3), Marwan Hariz (1), Ludvic Zrinzo (1)

1. Unit of Functional Neurosurgery, Institute of Neurology, UCL, Queen Square, London, United Kingdom

2. unit of Functional Neurosurgery, Institute of Neurology, UCL, Queen Square, London, United Kingdom

3. Unit of Functional Neurosurgery, Institute of Neurology, UCL, The National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom

Submitter: Mr Akram Harith (GB)

Introduction: Bowstringing may occur when excessive fibrosis develops around extension cables in the neck after deep brain stimulation (DBS) surgery. We have noted that this phenomenon only occurs when the cables crossed superficially over the convexity of the clavicle. We hypothesise that this adverse event may be avoided by directing the DBS extension cables towards the suprasternal notch.

Methods: When connecting DBS leads to an infra-clavicular pectoral implantable pulse generator, the tunnelling of the cables is directed medially, towards the region of the suprasternal notch, before being directed laterally towards the pectoral IPG pocket. In previously operated patients with established fibrosis, the fibrous tunnel around the DBS cables is opened and excised as far cranially as possible into the neck. Subcutaneous dissection allows rerouting of the cables medially, towards the suprasternal notch. Using the above approach, we reviewed our series of all patients who underwent DBS surgery over the last 10 years.

Results: In 429 patients, 7 patients (2%) with DBS cables tunnelled over the convexity of the clavicle complaining of bowstringing and tethering underwent exploration with release of the scar tissue over the clavicle and redirection of the cables medially towards the suprasternal notch. Revision of cable trajectory using the described method has eliminated bowstringing and provided better cosmetic results. In patients in whom cable trajectory was initially directed towards the suprasternal notch, we did not observe any bowstringing complaints.

Conclusion: Trajectory of tunnelling appears to have an impact on the postoperative incidence of fibrosis associated with DBS cables. Modifying surgical technique may reduce the incidence of this troublesome adverse event after DBS surgery.

#156

Reuse of internal pulse generator in infected cases after deep brain stimulation surgery

Selcuk Gocmen (1)

1. Neurosurgery, Pamukkale University, Denizli, Turkey

Submitter: Mr Gocmen Selcuk (TR)

Introduction: Deep brain stimulation (DBS) hardware-related infection is one of the most serious complications, and may need additional interventions. DBS is part of a growing group of expensive implantable devices. We improved this study to reuse the internal pulse generator (IPG) after DBS infection, and to reduce the economic costs.

Methods: A database of 102 patients who underwent DBS surgery was used in the study. Incidence, clinical characteristics and management of infections while reusing the IPG after DBS infection were analyzed and reported.

Results: The overall infection rate was 5.9% (6 of 102 patients) of the patients. The median time of infection was 3.5 months (range 1-6 months). The management consisted on total hardware removal followed by intravenous antibiotics. These patients recovered with no clinical signs of infection. In all patients, the IPG was infected. Staphylococcus was the causative organism. These patients underwent reimplantation surgery at least 3 months after completion of antibiotic treatment to reimplant the devices. Explanted IPGs were used in all cases and no hardware related infection or other complications were observed after reimplantations. The mean follow-up period was 14 months (range 6 month-24 months).

Conclusion: Management of hardware-related infections can be challenging. Removal of the infected device is generally needed to establish cure of infection of the DBS. The medical and economic cost of these infections is enormous. The IPG can often be saved in infected patients. Thus, a significant cost burden is eliminated. Properly executed, reuse of IPG should markedly reduce the cost of these devices.

#161

Twiddler's syndrome in a patient with dystonic tremor treated with DBS

Patric Blomstedt (1), Jennifer Samuelsson (1)

1. Department of neurosurgery, Umeå University Hospital, Umeå, Sweden

Introduction: Twiddler's syndrome is a rare complication of DBS. This condition occurs when the IPG is consciously or inadvertently rotated in its pocket, resulting in torsion and possible dislodgment of implanted electrodes, with subsequent loss of function.

Methods: We present a case of Twiddler's syndrome.

Results: A patient with bilateral Gpi DBS presented with straining cables at the neck five months after surgery and an x-ray demonstrated Twiddler's syndrome. Initial revision with preventive measures proved futile. After some time the condition recurred, now with dislocation of one of the intracerebral electrodes. In a second revision the IPG was placed under the pectoralis muscle, which has so far prevented further rotation.

Conclusion: While Twiddler's syndrome is fairly uncommon, it remains to be a risk associated with DBS. Recognizing the potential risks and signs might allow for preventive measures avoiding dislocation of the intracerebral electrodes.

#181

Initial experiences with intraoperative computed tomography (O-arm) in deep brain stimulation surgery

Edurne Ruiz de Gopegui (1), Gaizka Bilbao (1), Imanol Lambarri (2), Elena Lezcano (3), Juan Carlos Gomez (3), Beatriz Tijero (3), Olivia Rodriguez (4), Rafael Villoria (4), Ibai Diez (5), Iñigo Pomposo (1)

1. Neurosurgery, Cruces University Hospital, Barakaldo, Spain

2. Neurophysiology, Cruces University Hospital, Barakaldo, Spain

3. Neurology, Cruces University Hospital, Barakaldo, Spain

4. Neuroradiology, Cruces University Hospital, Barakaldo, Spain

5. Biocruces Institute, Cruces University Hospital, Barakaldo, Spain

Introduction: Deep brain stimulation is a well-known therapy for an increasing number of conditions. Its efficacy is highly dependent on the location of the electrodes on a particular target. Intraoperative microelectrode recording for targeting has been widely evaluated. Intraoperative images might offer additional information in order to establish the actual location of the lead. The aim of this study is to describe the use of intraoperative computed tomography (iCT) to confirm the lead location before surgical closure and to study the accuracy of this technique, compared to the post-operative MRI. Additionally, operating room settings as well as our learning curve and timing are shown.

Methods: Thirty-six consecutively implanted electrodes were prospectively studied in 22 patients undergoing DBS surgery using the O-arm system at Cruces University Hospital. Leksell frame was used and implantation was driven by the use of MER. A 1.5T MRI was performed within the first 24 hours after surgery. Surgical time was defined from skin incision to closure. 3DSlicer software was used for image analysis.

Results: Positioning of the patient on the operating table adapted to the O-arm demands a learning curve, with a median time in our series of 21 minutes. We usually find that hypothesis regarding the location of the lead by MER is sustained by the iCT. On average, 2.7 CT scans were performed per procedure, with a mean time of exploration of 13 minutes. The mean euclidean distance between the lead in the intraoperative final CT and the postoperative MRI is 1.58 millimeters (95% CI: 1.29 – 1.86). We found no statistical significant difference in measuring the euclidean distance at the distal lead tip or at the first lead contact ($p=0.247$).

Conclusion: We present here our initial series of patients undergoing DBS surgery using iCT. With the exception of the first procedures, we have found that it does not add significant length and can provide some valuable data in decision-making. It can be noted that intraoperative images correlate well with the postoperative MRI and that brain shifting can be considered minimal. This technology may prove useful therefore for targets where MER is not eligible.

#183

Early outcomes after frameless DBS placement in the intraoperative MRI suite

Darlene A Lobel (1), Danilo Silva (1), Andrei Barborica (2)

1. Neurosurgery, Cleveland Clinic Foundation, Cleveland, United States

2. FHC Europe, FHC, Inc., Bucharest, Romania

Introduction: DBS procedures may be performed using a variety of techniques, including frame-based and frameless systems. Often these surgeries are performed using microelectrode recording (MER) techniques to refine targeting and compensate for stereotactic positioning error. For select patients, DBS electrodes may be placed without MER, using intraoperative imaging to guide electrode placement. Frameless electrode placement guided by intraoperative imaging is an emerging technology that has been studied on only a limited basis to date. We present early outcomes data from the largest series of patients in whom DBS electrodes were placed using a frameless system in an intra-operative MRI Suite.

Methods: Eight patients underwent frameless DBS lead placement using intraoperative MRI (VISIUS Surgical Theatre, IMRIS Inc, Minnetonka, Minnesota) for the treatment of movement disorders. Seven patients were diagnosed with Parkinson's Disease, and one patient was diagnosed with myoclonus-dystonia. Intracranial fiducial markers were placed and MRI and CT scans were obtained between one and three weeks prior to the planned surgery. Direct targeting, based on fused images from pre-operative MRI and CT scans, was used for stereotactic planning. An MRI-compatible custom stereotactic fixture (STarFix™, FHC Inc, Bowdoin, Maine) was created for each patient, to guide electrode placement. Surgery was performed under general endotracheal anesthesia (GETA). Intraoperative MRI was obtained with the MRI-compatible ceramic cannulae and stylet fully inserted, to the target point. Images were fused to the surgical plan intra-operatively to assess accuracy of placement, using the Waypoint Navigator (FHC Inc) planning software. Stereotactic accuracy on the x, y, and z trajectory-aligned axes was calculated between planned target and tip of the cannulae. When necessary, adjustment of targeting was made either to correct for stereotactic error, or as a result of improved imaging quality under GETA. DBS electrodes were then inserted, and stimulation testing was performed intra-operatively to assess for stimulation effect in the internal capsule. Immediate post-operative MRI with DBS leads in place was obtained and images were fused to the surgical plan. Follow up examination was performed in an outpatient setting. Medication reduction and clinical benefit were assessed post-operatively.

Results: A total of fourteen electrodes were placed, eight in the globus pallidus internus (GPi), and six in the subthalamic nucleus. Intraoperative MRI revealed an average overall positioning error of 1mm compared to the planned target. Error was most significant along the z-axis. Eight electrodes were repositioned based on intraoperative images. Stimulation testing revealed a capsular effect at 7 Volts for one GPi electrode. No electrodes were repositioned based on stimulation testing. Post-operative MR images demonstrated DBS leads within 0.4mm of target. In short-term follow up of 1-7 months, no surgical complications have been observed. Movement disorder medications were reduced in 4 out of 5 patients who were at least 3 months post-implant. Average medication reduction in this group is 66%. Improvement in tremor, rigidity, and bradykinesia was noted in all 5 of these patients.

Conclusion: Frameless DBS electrode placement guided by intraoperative MRI offers a safe and effective alternative to MER-guided DBS surgery in short-term follow up.

#198

Combined pallidal and thalamic stimulation for multifocal primary dystonia with prominent writers' cramp

Joachim Krauss (1), Christoph Schrader (2), Götz Lütjens (1), Mahmoud Abdallat (1), Andreas Wloch (1)

1. Neurosurgery, Hannover Medical School, Hannover, Germany

2. Neurology, Hannover Medical School, Hannover, Germany

Introduction: The globus pallidus internus (GPi) has been established as the contemporary target for deep brain stimulation (DBS) in dystonia. The thalamic Vim, however, has been preferred in patients with writer's cramp. When a patient presents with both writer's cramp and other dystonic symptoms, it is unclear which target should be chosen. Multifocal DBS is a new treatment option which can address this issue.

Methods: A 23-year-old woman with multifocal primary dystonia and prominent writers' cramp underwent bilateral stereotactic implantation of DBS electrodes in the GPi and the thalamic Vim. Electrode location was confirmed by postoperative stereotactic CT. All four electrodes were connected to an implantable pulse generator. Assessment included the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), 36-item short-form health score (SF-36) and standard video recording. In the frame of a prospective study protocol clinical outcome was assessed before and at 3, 15 and 24 months after surgery.

Results: Thalamic stimulation yielded an improvement in writer's cramp of about 80% according to the BFMDRS. At 3 months follow-up the BFMDRS motor score had decreased from 3 before surgery to 0 and the disability score had decreased from 6 to 2. At the same time the SF-36 had improved from 31 to 78. The effect lasted for one year. At 15 months follow-up dystonia became more generalized, the BFM motor score had increased to 10 and the disability score to 6. The SF-36 had decreased to 67. The patient presented with an increase in dystonia of the right hand and the right foot accompanied by pain. Vim thalamic stimulation did not have a marked impact on the severity of dystonia. GPi stimulation improved slightly the dystonic symptoms in the right foot but did not address the writer's cramp. Finally by combined thalamic and pallidal stimulation both writer's cramp and the dystonic foot were improved. The effect was sustained at 24 months follow-up (40% improvement in BFM motor score).

Conclusion: In patients with multifocal primary dystonia and prominent writer's cramp combined thalamic and pallidal stimulation might yield additional benefits.

#205

Cessation of deep brain stimulation for secondary parkinsonism may result in a neuroleptic-like malignant syndrome

Tamara Sauer (1), Mark Wolf (2), Goetz Luetjens (3), Hans-Holger Capelle (4), Hansjoerg Baezner (5), Michael Hennerici (1), Joachim K. Krauss (4), Christian Blahak (1)

1. Neurology, University School Mannheim, Mannheim, Germany

2. Neurology, Medical School Mannheim, Mannheim, Germany

3. Neurosurgery, Medical School Hannover, Hanover, Germany

4. Neurosurgery, Medical School Hannover, Hannover, Germany

5. Neurology, Bürgerhospital, Stuttgart, Germany

Objective: To describe a rare life-threatening complication of complete battery depletion in a patient with deep brain stimulation (DBS) of the subthalamic nucleus (STN) for secondary parkinsonism.

Introduction: Neuroleptic malignant syndrome is characterised by the impairment of consciousness, high fever, rhabdomyolysis, rigidity and autonomic dysfunction. Although originally described in patients taking neuroleptic drugs, this syndrome may also occur in patients with Parkinson's disease during withdrawal or reduction of dopaminergic drug therapy and is called neuroleptic-like malignant syndrome or Parkinsonism–hyperpyrexia syndrome (PHS). To our knowledge this is the first case report of PHS following battery depletion in DBS for parkinsonism.

Methods: Case report.

Results: Our patient is a 48-year old man treated successfully with bilateral STN-DBS since 2004 because of a complex movement disorder due to infantile hypoxic brain damage showing a generalized hypokinetic-rigid syndrome with resting tremor of the arms and head, but also segmental dystonia with torticollis and orofacial dyskinesia. He was admitted to our hospital with an acute exacerbation of the movement disorder, moderate fever and tachycardia. The implanted pulse generator showed complete battery depletion. Although immediately treated with antipyretics, dopaminergic drugs, sedatives and anticholinergics, the patient quickly develops severe hyperthermia up to 41°C, rhabdomyolysis, renal failure and fluctuating delirium. The subsequently performed battery replacement improved rigidity, tremor and dyskinesia to some extent, but during the course of hospitalisation the patient developed bilateral aspiration pneumonia requiring mechanical ventilation and tracheostomy, thrombopenia, intermittent atrial fibrillation and severe critical illness polyneuropathy. About a month after admission the patient was transferred to a rehabilitation facility with improved control of the movement disorder, but fluctuating level of consciousness, flaccid tetraparesis, and still Intermittent mandatory ventilation.

Conclusion: This case shows impressively that PHS may occur as a life-threatening medical emergency in patients with a sudden cessation of DBS for parkinsonism.

#206

Comparative study of emotional prosody following subthalamic nucleus Deep Brain Stimulation (DBS) for Parkinson's Disease

Dimitra Kastamoniti (1), Miltiadis Georgiopoulos (2), George Sakellariopoulos (1), Constantine Constantoyannis (2)

1. Department of Medical Physics, Faculty of Medicine, University of Patras, Patras, Greece

2. Functional Neurosurgery Unit, Department of Neurosurgery, Faculty of Medicine, University of Patras, Patras, Greece

Introduction: Despite the predominance of movement disabilities, symptoms of Parkinson's disease (PD) extend well beyond motor abnormalities. Speech is affected in various ways and prosody, i.e. the rhythm, stress, and intonation of speech that reflect its emotional content or emphasis, is disrupted. Recently, the effect of subthalamic Deep Brain Stimulation (DBS) on voice and speech of PD patients has gained scientific interest. In the present study we investigate the possible differences in both the perception and expression of prosody between the stimulation (DBS-On) and non-stimulation state (DBS-Off) of PD patients.

Methods: The perception of emotional prosody was studied in 16 patients (12 male, 4 female, mean age: 65.1 ±7.8 years) with idiopathic PD and chronic bilateral subthalamic DBS that were not under the influence of dopaminergic medication during the tests. The stimulation settings were previously optimized for best overall motor performance.

The patients were asked to select the correct prosody from a list, after they listened to a specific word and then a specific sentence that were recorded previously with different prosodies (word: neutral, interrogative, sadness, sentence: neutral, interrogative, anger, admiration) by a professional announcer. The process was performed initially in DBS-On state and then in DBS-Off state and it was then repeated in the reverse order and with a different sequence of recordings.

The word "yes" and the sentence "Maria goes to university", both in the Greek language, were used for the measurements. The purpose of using the specific word was that is widely used in the vocabulary of the Greeks and can change the meaning of the speech depending on the prosody that it takes. The sentence was created to cover several emotions by changing prosody.

The expression of emotional prosody of the same PD patients was studied at another session. They once again listened to the aforementioned recorded material (in a different order) and then they were asked to repeat exactly what they heard. Their voice was recorded, and their intonation was evaluated by 50 normal listeners that were aware of the announcer's prosody. The listeners rated the PD patients' intonation with an informal assessment scale from 1 (no comprehension of the aimed prosody) to 6 (excellent comprehension). This process was performed in both DBS states.

The perception of emotional prosody was analyzed using the z-statistic for comparison of proportions. The expression of emotional prosody was studied using either the paired t-test or the Wilcoxon signed rank test, according to the results of appropriate tests for the assumption of normality.

Results: The percentage of correct perception of prosody ranged from 31.3% (sentence: admiration) to 62.5% (sentence: interrogative) and did not differ significantly between DBS-On and DBS-Off states. An investigation of the incorrect perceptions of prosody, however, showed a significantly worse response of the DBS-On state when the recorded prosody was neutral while, on the other hand, patients in DBS-On state performed significantly better when the initial prosody was interrogative.

Regarding the expression of emotional prosody, mean evaluations among the normal listeners ranged from "inadequate comprehension" (sentence: anger, admiration) to "very good comprehension" (sentence: neutral, word: interrogative). Compared to DBS-On state, the expressed prosody of PD patients in DBS-Off state was significantly better perceived in sentences expressing anger and admiration or were of neutral prosody, as it was also the case of the single word of neutral prosody.

Conclusion: In our study, perception of prosody showed no consistent behavior under stimulation states. The expression of prosody, on the other hand, seems to deteriorate when stimulation is applied. These findings are in line with other studies that have reported inconsistent results. Further investigation is needed, especially in terms of a larger sample size and the inclusion of acoustic measures of speech analysis.

#208

Deep brain stimulation for dystonia in patients with previous thalamotomy/subthalamotomy or pallidotomy and peripheral denervation

Goetz Luetjens (1), Hans-Holger Capelle (2), Christoph Schrader (3), Joachim K. Krauss (2)

1. Neurosurgery, Medical School Hannover, Hannover, Germany

2. Neurosurgery, Medical School Hannover, Hannover, Germany

3. Neurology, Medical School Hannover, Hannover, Germany

Introduction: In patients with severe segmental dystonia both pallidotomy and thalamotomy/subthalamotomy was used in the past. Little is known about the outcome of pallidal DBS in patients in whom pallidotomy or thalamotomy/subthalamotomy and peripheral denervation loses effect.

Methods: We report on two patients who had radiofrequency lesioning and underwent subsequent DBS. The first patient with segmental dystonia had repeated bilateral pallidotomy and peripheral denervation procedures. After loss of efficacy he underwent pallidal DBS. The second patient with cervical dystonia had unilateral thalamotomy/subthalamotomy and peripheral denervation procedures before he underwent pallidal DBS.

Results: Follow-up time was 40-52 months. In the first patient marked improvement was seen after pallidal stimulation reflected in the amelioration of the BFMDRS motor score from 53 to 9.5. In the second patient the BFMDRS motor score improved from 6 to 4 and the TWSTRS torticollis severity score improved from 23 to 14 during long-term follow-up.

Conclusion: Patients who had prior pallidotomy or thalamotomy/subthalamotomy and peripheral denervation procedures for segmental and cervical dystonia can experience further improvement from subsequent pallidal DBS. Patients with previous pallidotomy may respond better than with previous thalamotomy. These patients should therefore not be excluded from subsequent DBS surgery.

Quality of Life in Advanced Parkinson's Disease after Bilateral Subthalamic Stimulation: 2 Years Follow-up Study.

Michał Sobstyl (1), Mirosław Ząbek (1), Wojciech Górecki (1), Zbigniew Mossakowski (1)
1. Neurosurgical Department, Postgraduate Medical Center, Warsaw, Poland

Objectives: The aims of this study were to assess the quality of life (QoL) using Parkinson's Disease Questionnaire PDQ-39 after bilateral subthalamic deep brain stimulation (STN DBS), and to identify correlations between changes in UPDRS score and separate PDQ 39 QoL dimensions and PDQ summary index (SI) score at long-term follow-up.

Methods: We evaluated 16 patients with advanced PD after bilateral STN DBS. All 16 patients were assessed 1 year after surgery and 14 were studied 2 years after surgery. The patients were assessed using Unified Parkinson's Disease Rating Scale (UPDRS) in medication-on and medication-off conditions, both preoperatively and postoperatively. All UPDRS evaluations were performed postoperatively during stimulation-on condition. QoL levels were determined by applying PDQ-39 questionnaire.

Results: The UPDRS scores after 1 and 2 years in medication-off and -on conditions when bilateral STN DBS was switched on showed a significant difference between baseline scores and follow-up scores (both in -off and -on conditions) in every UPDRS measurement except for mentation after 2 years. Most of p-values indicated that the differences were highly significant ($p < 0.01$) based on Wilcoxon signed-rank test. All dimensions of PDQ-39 as well PDQ-39 SI score were highly significantly improved after 1 year. The same improvements were visible in 2 years follow-up with the exception of social support and communication. We found a positive correlation between ADL UPDRS, motor off UPDRS scores and PDQ-39 ADL and PDQ-39 SI scores. A further analysis of separate motor PD features revealed that tremor, bradykinesia and axial features were correlated with improvements mostly seen in PDQ-39 ADL and PDQ-39 SI scores. Moreover, in medication-on condition, we found a strong correlation between dyskinesia UPDRS score and PDQ-39 mobility, ADL, and PDQ-39 SI score. We observed a negative correlation between improved fluctuation UPDRS score and PDQ-39 mobility. We identified no correlation between the duration of the off period and levodopa dose and changes in PDQ-39.

Conclusion: STN DBS significantly improved important aspects of QoL as measured by PDQ-39. The improvements were maintained at 2 years follow-up except for social support and communication. We demonstrated a positive correlation between changes in the off condition of motor UPDRS scores and dyskinesia UPDRS scores in several PDQ-39 dimensions, whereas fluctuation UPDRS scores were negatively correlated with PDQ-39 mobility scores.

#212

Staged bilateral thalamotomy for musician's dystonia

Takaomi Taira (1), Shiro Horisawa (2)

1. Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

2. Neurosurgery department, Tokyo Women's Medical University, Tokyo, Japan

Introduction: There have been some reports about unilateral thalamotomy for focal hand dystonia and thalamotomy provides rapid and long-acting effect. About half a century ago, there were many reports about severe complications of bilateral thalamotomy for Parkinson's disease, such as altered consciousness, personality change, and death. With the advent of deep brain stimulation, the number of bilateral thalamotomy progressively declined. However, the risk of old thalamotomy with no use of CT and MRI remains a matter of research.

Methods: We describe two patients with bilateral focal hand dystonia who underwent staged bilateral thalamotomy without severe complications.

Results and conclusion: This report suggests that staged bilateral thalamotomy is a feasible procedure with strict selection of patients and modern technique of stereotactic functional neurosurgery. To the best of our knowledge, this is the first report about bilateral thalamotomy for musician's dystonia.

#214

Fingertapping 5 year postoperatively is performed in similar speed with DBS on without antiparkinsonian medication as before surgery in the L-dopa challenge test

Natalie Montevert (1), Ursula Albert (2), Hjalmar Bjartmarz (1), Anna-Lena Törnqvist Jensen (3)

1. Department of Neurosurgery, Skåne University Hospital, Lund, Lund, Sweden

2. Department of Psychiatry, Skåne University Hospital, Lund-Malmö, Sweden

3. Department of Neurosurgery, Skåne University Hospital, Lund, Lund, Sweden

Objective: Investigate if the finger tapping after five years of STN DBS treatment is different from the preoperative defined on test in patients with Parkinson's disease (PD),

Introduction: Timed tests can be seen as less subjective assessments as compared to UPDRS III, even though they also are afflicted with possible errors. Positive long term effects of STN DBS in PD has been shown as assessed with UPDRS III, but there has been limited reports on the long term effects measured with quota scale (i.e. time or number).

Methods: Thirty eight patients (10 women) who had done their routine 5-years follow up were included. At the time of surgery they have had PD for 14 years (sd 6 years) and were 63 years (sd 7 years) old. At the 5 year follow-up antiparkinsonian medication were still lower as compared to preoperatively ($p < 0.0001$). They were examined in defined off and on preoperatively, and in the same condition postoperatively but also with DBS turned off and on. Finger tapping was performed by moving the index finger between two squares 30 cm apart during 60 seconds. DBS was turned off 45 minutes before the tests and on for >24 h.

Comparisons were made between preoperative defined on and postoperatively in defined off with DBS on (i.e. DBS own effect) and defined off preoperatively with defined off and DBS off.

Results: Five years postoperatively there were no significant differences ($p > 0.9$) in numbers of finger tappings during 60 seconds with DBS on in defined off as compared to preoperative defined on. Neither were there any significant differences with DBS off in defined off with the preoperative defined off test. However, DBS substantially increased ($p > 0.0001$) the number of finger tapping as compared to the defined off state preoperatively as well as at five years). The DBS settings were changed between one and five years postoperatively ($p < 0.0001$). In terms of other motor assessments (UPDRS III) a suggestion of disease progression ($p < 0.001$) can be seen at five years postoperatively, but DBS alone still reduces the symptoms significantly ($p < 0.001$).

Conclusion: This is a small sample, however indicating that the patients even five years after DBS surgery have similar effect as preoperative defined on in terms of fingertapping and gait, even though they are older and have had PD for five more years. Thus, the preoperative performance of finger tapping in defined on may be an indication for performance even in long term.

#215

Paroxysmal cough attacks with syncope induced by thalamic DBS for essential tremor

Bernhard Décard (1), Ethan Taub (2), Peter Fuhr (1)

1. Neurology, University Hospital Basel, Basel, Switzerland

2. Neurosurgery, University Hospital Basel, Basel, Switzerland

Introduction: Deep brain stimulation (DBS) in the nucleus ventrointermedius of the thalamus (VIM) is a safe and effective treatment for medically refractory essential tremor. Its most common side effects are dysarthria, dysphagia, paresthesiae, and unbalanced gait. Coughing occurs rarely during DBS implantation procedures, probably because of venous air embolism, but has not previously been reported as a side effect of stimulation per se. We present the case of a patient with persistent cough attacks, sometimes followed by syncope, which were induced by thalamic deep brain stimulation.

Case description: The patient, a 66-year-old man with a family history of essential tremor, had suffered from progressively severe tremor for two decades. The tremor was of an action-postural and kinetic type and affected mainly the upper limbs; there were no other extrapyramidal signs or symptoms. Although unaffected by alcohol, the tremor was otherwise typical of essential tremor. It responded well at first to treatment with primidone, but, by the time of presentation to us, could no longer be adequately suppressed by primidone in doses of up to 750 mg/day. Treatment with propranolol was contraindicated by bronchial asthma. His asthma was well controlled with fluticasone and formoterol except for rare cough attacks, which were sometimes followed by syncope. He declined further trials of drug treatment for tremor (e.g., with topiramate), and the tremor became severe enough to interfere with the activities of daily living. In December 2013, he underwent the implantation of a DBS system with electrodes in the VIM on both sides, without complication. His tremor improved markedly under DBS, and primidone was tapered to off. He complained of mild dysarthria and dysphagia under stimulation at high amplitudes; therefore, two DBS settings were programmed into his device (program A: 2.9/3.0 V [right/left], program B: 2.2/2.3 V, pulse width 90 µs and frequency 130 Hz for both A and B). He was able to switch back and forth between the two programs at will, in a situationally appropriate manner, using the patient programmer. Under active stimulation at either of these settings, he reported the frequent (almost daily) occurrence of paroxysmal cough attacks, some of which were followed by syncope, occurring particularly in the evening while he reclined in an armchair. He also noted that the frequency of cough attacks was related to the DBS amplitude (program A versus program B). The doses of his anti-asthma drugs and other medications had not been changed since before DBS implantation. To treat the cough attacks, the stimulation amplitudes were lowered (program A to 1.8/1.8 V, program B to 1.2/1.2 V) and he was given the opportunity to set his stimulation to program A, program B, or off. Under this regime, his tremor remained under satisfactory control, and paroxysmal coughing became rare again.

Conclusion: Earlier reports cough in relation to DBS have exclusively concerned intraoperative coughing during implantation procedures, which is thought to be caused by small venous air emboli. To our knowledge, this is the first report of severe cough directly related to thalamic DBS per se. Pre-existing lung disease (e.g. asthma, as in our case) might be a risk factor for DBS-related cough attacks. Although this phenomenon is presumably rare, physicians should be aware of it because of the associated danger of medical complications, such as syncope and aspiration pneumonia.

#222

Advantage of axillary skin incision for implantation of deep brain stimulator

Takeshi Nakajima (1), Takehiko Konno (1), Rie Nagayama (1), Yoshihito Ando (2), Hidenori Yokota (1), Keiji Oguro (1), Kenichi Fujimoto (2), Eiju Watanabe (1)

1. Department of Neurosurgery, Jichi Medical University, Tochigi, Japan

2. Department of Neurology, Jichi Medical University, Tochigi, Japan

Submitter: Mr Nakajima Takeshi (JP)

Introduction: Implantable pulse generator (IPG) for deep brain stimulation (DBS) often surgically implanted via skin incision on anterior chest wall. However, this technique is apparently inferior in regard to cosmetic consequence, and axillary incision has been recently proposed as alternative

Methods: This case report stressed the advantage of axillary incision, not only in cosmetic aspect but durability to traumatic external forces.

Results: 62-year-old gentleman with DBS therapy for seven years underwent the exchange of IPG due to its empty of life. The skin incision on anterior chest wall, originally done in the first implantation seven years ago, was reopened for the exchange. Several days after discharge, he fell twice and the traumatic direct force on the anterior chest caused unexpected dissection of the surgical scar. The IPG was exposed and contaminated, then eventually removed.

Conclusion: Parkinson's disease often disturbs gait and postural reflex, and falls would become critical problem in the patients. Surgical scar on the anterior chest is prone to directly bump when the patients fall. From this point of view, axillary incision is considered to be more suitable technique since it prevents the scar from direct force and injury.

#225

Deep Brain Stimulation Programming Experiences for Non-Motor Complications in Parkinson's Disease

Peter Poortvliet (1), Karen O'Maley (2), Terry Coyne (3), Peter Silburn (4),
 1. Asia-Pacific Centre for Neuromodulation, University of Queensland, brisbane, Australia
 2. Neurosciences Queensland, St Andrew's War Memorial Hospital, Brisbane, Australia
 3. Brizbrain, University of Queensland, brisbane, Australia
 4. Neurosciences Queensland, University of Queensland, brisbane, Australia
 5. Asia-Pacific Centre for Neuromodulation, University of Queensland, Brisbane, Australia

Introduction: Parkinson's disease (PD) is a severely disabling, progressive neurodegenerative disorder characterised by cardinal motor symptoms such as tremor, rigidity or bradykinesia as well as gait and posture disturbances. However, non-motor symptoms including mood disturbances are also common in PD, although not always appropriately identified by the patient or during clinical evaluations. Mood changes may reflect changes in disease-progression, pre-existing psychiatric history, but can also be caused or aggravated by medical or surgical PD treatments. Deep brain stimulation (DBS) targeting the subthalamic nucleus (STN) is a well-established surgical intervention for the treatment of PD. Although DBS has proven to be a safe and effective treatment option for reducing many motor symptoms of PD, mood disturbances have also been observed affecting the patient and in most cases their significant others. A possible explanation for post-surgical mood disturbances is that nearby structures are affected by the distribution of the electric field surrounding the electrode contacts. DBS electrodes consist of four closely spaced contacts that can be individually activated (i.e., standard monopolar, with one contact as cathode and the neurostimulator case as anode) or in pairs (i.e., bipolar, with one contact as cathode and another contact as anode). Adjusting the electrical parameters of the active contacts can further optimize the therapeutic effects of stimulation (i.e., voltage, pulse width, and frequency). The challenge with STN DBS is to find the optimal contact configuration and programming strategy to maximise motor symptom benefit, but also to identify non-motor symptoms and minimise their effects.

Methods: We report four clinical observations (3 male, 1 female) where post-surgical standard programming practices of STN DBS showed considerable improvement of motor symptoms, however, patients also presented with self-reported mood disturbances. Although subsequent stimulation strategies improved therapeutic effects for mood they proved unsuccessful to adequately retain improvement of motor symptoms. In the period following the procedure, all possible standard DBS configurations and parameters were tested in these four patients, with no satisfactory result. Post-operative scans of electrode placement revealed that the mood effects could be caused by the proximity of optimal bottom contacts to the limbic STN. During subsequent programming consultations patient configuration settings were changed to bipolar and the polarity of the optimal active contacts was reversed. Reversing the polarity resulted in a redistribution of the electric field with an upward shift of stimulation area away from the limbic STN.

Results: All four patients reported reductions in mood disturbances with some reporting a subsequent reduction in motor symptom control. Motor symptom control was subsequently addressed by increasing the voltage settings over a four-week period of observation, without the risk of re-introducing mood disturbances.

Conclusion: These four cases highlight the need for discussion and development of trials to determine best clinical practice for identification and management of mood disturbances and related programming methods.

#226

Effect of intraoperative narrowing of the third ventricle on the electrode implantation site in DBS surgery

Jens Fichtner (1), Markus Oertel (1), Andreas Nowacki (1), Michael Fiechter (1), Ines Debove (2), Lenard Lachenmayer (2), Michael Schüpbach (2), Claudio Pollo (1)

1. Neurosurgery, Inselspital Bern, University of Bern, Bern, Switzerland

2. Neurology, Inselspital Bern, University of Bern, Bern, Switzerland

Submitter: Mr Fichtner Jens (CH)

Introduction: Brain shift during deep brain stimulation (DBS) surgery can be caused by cerebrospinal fluid (CSF) loss and can be a considerable problem for the precise implantation of DBS leads, especially on the second side. In this study, we want to study the intraoperative variation of the width of the third ventricle and the effect of this variation on the final position of the definitive DBS lead on the second side of surgery.

Methods: We included 83 patients selected for bilateral DBS surgery from 2012 to 2014. We measured the width of the third ventricle in preoperative frame based computer tomography (CT) and compared it to immediately postoperative frame based CT. The width of the third ventricle was measured at the level of the mid commissural point. The targeting was performed on MRI based targeting and co-registered stereotactic CT. The site of implantation of the DBS lead was decided according to micro-recording and intraoperative clinical testing through the Ben-Gun. Patients not implanted in the symmetrical trajectory on the second after implantation of the first side were considered.

Results: Postoperative results were measured in 70 patients. Seven patients were excluded because of artifacts that made it impossible to measure the postoperative diameter of the third ventricle. In six patients postoperative CT data was not available. The preoperative width (mean $6.82 \pm \text{SD } 2.92\text{mm}$) of the third ventricle was significant larger than the postoperative diameter (mean $5.64 \pm \text{SD } 2.79\text{mm}$); $p=0.014$, (t-test for independent samples). After clinical testing, 25.6% of the cases implanted on the first side were not symmetrically implanted on the second side. Of these, 70% were more medial, 20% more lateral and 10% in anterior/posterior direction in contrast to the first implanted side.

Conclusion: Intraoperative CSF loss results in narrowing of the third ventricle in DBS patients, subsequently impacting the site of implantation of the definitive DBS lead on the second side. These findings suggest that intraoperative micro-recording and clinical testing are useful to detect a mapping asymmetry between both sides. Efforts should be made to avoid CSF loss during surgery. A bilateral simultaneous implantation may also prevent intraoperative brain shift during DBS surgery.

#228

Magnetic resonance safety in two DBS patients with Vercise©System, our experience report

Pedro De La Rosa Jiménez (1), Beatriz Cuartero Pérez (1), Ossama Morsi (2), Miguel Ángel Pérez-Espejo Martínez (1), Juan Francisco Martínez-Lage Sanchez (1)

1. Neurosurgery, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain

2. Neurology, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain

Introduction: Magnetic resonance is nowadays the favorite verify test after the DBS surgery in many centers around the world. It gives you good imaging about the real localization of the electrodes after the surgery and allows you to see the absence of bleeding.

Methods: In our case, we usually use it with the traditional systems from Medtronic, Kinetra© either Activa PC©, without any problem. Nevertheless, with the introduction of Vercise©, from Boston Scientific, in our hospital, we have had to change our verify test to CT-scan according with the manufacturer specifications. Even so, in two cases we have performed an MRI with it after surgery, having good results, and without any related to it problem.

Results: Our first patient was a fifty-seven aged female with PD for eight years. At the moment of undergoing DBS she had very severe tremor in both superior limbs besides very dependent basal situation for her disease. As usual protocol, we performed an MRI days before the surgery, then a CT-Scan with Leksell Frame in surgery morning, we fused both images, and, under local anesthesia, we located the electrodes in the postero-lateral part of STN by helping us with MER and clinical examination during intra-operative stimulation, with good intra-operative results. We put the IPG then under general anesthesia infra-costal as usual. Twenty-four hours after the surgery, as a part of our protocol, we performed an MRI with the IPG turned off that showed good location of electrodes without any complication. Patient was discharged few days after that with no problems related to the MRI.

The second one, a sixty one aged male, who underwent DBS one year previously, but with very bad results due to adverse effects of stimulation, which compelled us to remove it after some months. We performed DBS with usual protocol. Despite a good pre-surgical MRI, MER and clinical examination during surgery, results did not satisfy us. So, after few tracks, and in order to avoid the increase of bleeding risk, we performed MRI with Leksell frame and MRI localizer to see where our electrodes really were. In spite of a not so good MER, MRI showed us adequate location of electrodes that made us leave them in this place. We put then the IPG under general anesthesia. Patient was discharged one week later without any PD pharmacological treatment and with really very good response to stimulation.

Conclusion: In both cases we did not have any MRI related problem. MRI was performed with transmit-receive head coil in 1.5T MRI, and with limit specific absorption rate (SAR) as we normally do with other DBS systems.

In our opinion, MRI should be the gold standard verify test after DBS surgery, however, to confirm the total safety of our procedure, more cases must be performed in such a way.

#229

Use of Microrecording and Multiple Trajectories in Deep Brain Stimulation (DBS) of the Nucleus Subthalamicus

Daniela Falk (1), Jose W.L. Reis (1), Steffen Paschen (2), Nils Warneke (1), H.Maximilian Mehdorn (1)

1. Neurosurgery, University Hospital of Schleswig-Holstein, Campus Kiel, Kiel, Germany

2. Neurologie, University Hospital of Schleswig-Holstein, Campus Kiel, Kiel, Germany

Introduction: The need of intraoperative microrecording (MER) and the simultaneous use of multiple trajectories during DBS surgeries for the placement of electrodes in the subthalamic nucleus (STN) in Parkinson's disease is a point of ongoing discussion. In our department we used the microrecording in all cases. The aim of this study was, to control our advancement due to the possible benefit for the patients.

Methods: We retrospectively analysed all data of patients, which have undergone DBS-surgery for Parkinson's disease in our department in 2008 and 2009. We recorded the number of microelectrodes, the trajectory of the permanent electrode, the reasons for avoiding the central trajectory, the coordinates of the active contacts of the permanent electrode and the clinical outcome.

Results: In the 2 years period we performed bilateral stimulation of the STN in 80 patients with Parkinson's disease (160 procedures). We were able to use all 5 microelectrodes in 39,4% , and 3 or more in over 98,1%. For the permanent electrode the central trajectory was chosen in 44,4%, which means that we implanted 55,6% over periphery trajectories. Main reason was a better effect with sometimes just slight differences. Second reason was the border for side effects, which constrained us to avoid the central trajectory. Due to the microrecording we were able to identify the borders of the STN in all cases and thereby the longest and best-responding trajectory, which could then be used for shortened stimulation period. This helped for the procedure, but the decision was always made due to the intraoperative stimulation. The clinical results are in range of published data.

Conclusion: In our patient group we would have not reached the optimal target with a single trajectory guided by MRI in 55,6%. The microrecording is an additional tool for targeting, but the decision for the placement was done by the test stimulation. Test stimulation is shortened as usually only performed in the trajectory with the best recording results. In our opinion the simultaneous use of multiple trajectories is a reasonable tool for the optimal outcome of the patient.

#230

Effectiveness of zona incerta deep brain stimulation in tremors refractory to thalamic stimulation

Witold Libionka (1), Wojciech Kloc (1)

1. Neurosurgery, Copernicus Hospital, Gdansk, Poland

Introduction: Ventral intermediate thalamic nucleus (Vim) is the target of choice for deep brain stimulation in tremors refractory to medical treatment. Although response is excellent in majority of cases, especially of essential tremor, some patients respond poorly or develop resistance over time. This group looks for novel treatments.

Methods: Three patients, first with refractory Holmes tremor (HT) on the dominant right side secondary to thalamic infarct, second with bilateral multiple sclerosis tremor (MST) most pronounced in the right upper extremity, previously effectively treated with bilateral Vim DBS, presented with symptom recurrence, and third with bilateral MST most pronounced in the right upper extremity. Zona incerta deep brain stimulation (ZI DBS) was performed monolaterally in all patients (there was no response to intraoperative Vim macrostimulation and ZI was planned as secondary target in HT, while in Vim DBS resistant MST ZI was chosen as primary target and ZI macrostimulation was more effective than Vim stimulation in the third patient). All procedures were performed under local anesthesia with microrecording and macrostimulation. Patients were evaluated with the Fahn-Tolosa-Marín Tremor Rating Scale (FTMTRS) before and 1, 3, 6 and 12 months after surgery.

Results: All patients showed marked functional improvement (54% in FTMTRS after 1 months in HT maintained during further follow-up and 73% after 1 months in MST with moderate gradual deterioration to 58% after 12 months). Active contact coordinates in relation to mid-commissural point were 10.9, -3.6, -1.5 for HT, and 12 -6, -2 for MST.

Conclusion: ZI DBS is an important treatment option for tremors resistant to standard Vim DBS.

Acute transient severe dyskinesia following subthalamic nucleus stimulation

Mehmet Tonge (1), Nesrin Helvacı Yılmaz (2), Yasin Temel (3), Fatihhan Bolukbasi (1), İlhan Elmacı (1)

1. Neurosurgery, Istanbul Medipol University, Istanbul, Turkey

2. Neurology, Istanbul Medipol University, Istanbul, Turkey

3. Neurosurgery, Maastricht University, Maastricht, Netherlands

Introduction: Transient microlesion effects following deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients with Parkinson's disease is a known phenomenon, but not well investigated. Several patterns of acute postoperative microlesion effects have already been described including cessation of tremor, relaxation of rigidity, and improvement of akinesia. Acute severe dyskinesia following STN stimulation is a rare entity which seems to be related with better surgical outcome. Here, we report a case with this condition.

Results: A 58 year-old lady with Parkinson's disease for twenty years with prominent dyskinesia underwent bilateral STN-DBS in our clinic. She developed severe post-operative dyskinesia more significantly at the level of the head and neck, without the stimulation being turned ON. Levodopa doses were decreased and dyskinesia resolved on post-operative 2nd day. On post-operative first day, the stimulation was turned on and medication was increased gradually. She benefited significantly from surgery at all on further follow-ups. Her UPDRS scores improved significantly on nine-month follow-up.

Conclusion: Transient acute severe dyskinesia is a rare postoperative microlesion effect of STN-DBS. Previous case reports confirm this situation as a positive predictive value for surgical efficacy. We experienced similar results. In addition, microlesion effects can last up to several weeks. Although pathophysiological mechanisms remain unclear, the STN seems to be involved both in hypokinesia and hyperkinesia.

#232

The effect of deep brain stimulation on cognitive performance in patients with Parkinson's disease

István Valálik (1), Gyula Demeter (2), Ferenc Kemény (2), Ágnes Lukács (2), Mihály Racsmány (2)

1. Department of Neurosurgery, St. John's Hospital, Budapest, Hungary

2. Department of Cognitive Science, University of Technology and Economics, Budapest, Hungary

Introduction: There is a growing number of studies focusing on the short, medium and long term effects of deep brain stimulation (DBS) on motor and cognitive functions in Parkinson's disease (PD). Substantially smaller number of studies performed on the results of surgical treatment of drug-resistant tremor in patients with secondary Parkinson syndrome (PS).

In our study we aimed to assess the effect of DBS on main cognitive functions, depression and anxiety in PD and PS patients.

Methods: Ten PD patients with bilateral subthalamic-DBS and ten PS patients with bilateral thalamic Vim-DBS were evaluated before and after the surgery. Surgical planning was based on frameless MRI to CT image fusion with custom-developed Vister-3D planning software. The procedure was performed with guidance of RM and MHT stereotactic systems. Intraoperatively 3 to 5-channel microelectrode recording has been applied with registration of LeadTools (Medtronic) or Neurospot (Neurostar) recording equipment. Model 3389 electrodes were implanted bilaterally in all cases and connected to Activa PC or Kinetra dual channel implantable pulse generators.

Results/Conclusion: The electrode position has been controlled with postoperative CT to preoperative MRI and to tractography co-registration. The patients' cognitive performance level and clinical profile was compared not just to their own baseline, but also to a proper clinical control group, un-operated patients with PD and PS. The neuropsychological screening was focused on short term verbal and visuo-spatial memory, attention and executive functions. The possible relationships between area of stimulation, symptom severity and cognitive functioning will be discussed.

#234

Deep brain stimulation for pediatric dystonia secondary to cerebral palsy

Mehmet Tonge (1), Nesrin Helvacı Yılmaz (2), Guzide Turanlı (3), Yasin Temel (4), Ramazan Sari (1), İlhan Elmacı (1)

1. Neurosurgery, Istanbul Medipol University, Istanbul, Turkey

2. Neurology, Istanbul Medipol University, Istanbul, Turkey

3. Pediatric Neurology, Istanbul Medipol University, Istanbul, Turkey

4. Neurosurgery, Maastricht University, Maastricht, Netherlands

Introduction: Cerebral palsy (CP) is the most common cause of secondary dystonia in childhood. Dystonic movements in CP patients can severely disable patient and restrict daily activities. When refractory, surgery should be considered for to alleviate dystonic symptoms. We hereby present a pediatric patient who underwent deep brain stimulation (DBS) of the posteroventrolateral part of the globus pallidus internus (GPi) for secondary dystonia.

Results: An eight-year old girl with CP due to a premature birth followed by kernicterus. She has been treated with intense physiotherapy programs during childhood and has undergone several botulinum toxin injections on various sites of the body. Her dystonic movements have become more prominent in recent years although spasticity has been better controlled with oral baclofen and physiotherapy. Since the dystonic movements severely impaired the girl's general functioning and complicated the work of her caregivers, we performed bilateral GPi with informed consent from parents. In the early postoperative period, no clear positive effects were noticed. However, from three months on, clear effects were seen on general functioning and sitting balance.

Conclusion: However secondary dystonias are known less responsive to surgical interventions than primary dystonias – especially DYT-1 dystonia -, medical treatment options are also limited. Late improvement of symptoms following surgery up to couple of years has been reported in children. Surgical targets for secondary dystonia is a subject of discussion; some advocate Gpi, others subthalamic nucleus and some ventral-oral nucleus of thalamus. Another aspect of DBS in childhood is the ethical issues. Major superiority of DBS on lesioning procedures seems to be the reversibility of the procedure.

#240

First Experience of Bilateral Pallidotomy for the Treatment Chorea-Dystonia Patient to Improve Quality of Life in Indonesia

Tommy A. Nazwar (1), Achmad Fahmi (1), Agus Turchan (1)
1. Neurosurgery, Dr Sutomo General Hospital, Surabaya, Indonesia

Introduction: Chorea-dystonia occurs in up to 0,021% of representative community. Macalister, CJ made a classification for chorea due to its origin. But, there is little known about the percentage of patient with chorea-dystonia that was cure in Indonesia. This experience aims to notify the improvement of quality of life patient with chorea-dystonia after surgery in Indonesia.

Methods: This study using bilateral pallidotomy with stereotactic procedures for treatment chorea-dystonia patient was done in National Hospital, Surabaya, 2013. Data was collected to examine the patient with thrashing motion, which arise almost 4 years. The movements involve the face, trunk, neck and extremities. Movements are rapid, random, unpredictable, repeated and not rhythmic.

Results: Chorea-dystonia was confirmed before treatment. After bilateral pallidotomy, movements was significantly reduced, patient nearly performed normal activity in daily living. No post-operative complications were registered. (It has been documented with movie)

Conclusion: The authors describe their experience that bilateral pallidotomy can be choice for treatment chorea-dystonia to improve quality of life.

#243

Exploring the meaning of the Subthalamic Nucleus's neural signal in Parkinson.

Bergman Hagai (1); Fried Itzhak (2), Gurevich Tania (2), Giladi Nir (2), Endelman Fani (2), Manor Yael (2), Cohen Jacob (2), Balash Jacob (2), Zurbal Mika (2).

1. Medical Neurobiology Departement, Haddassa hospital, Jerusalem, Israel.
2. Movement disorder unit, Ichilov medical center, Tel Aviv, Israel
3. Neurosurgery departement, Rabin medical center, Tel Aviv university, Israel

Objective: Exploring the meaning of the Subthalamic Nucleus's neural signal in Parkinson.

Methods: We studied the impact of the neurophysiological and surgical properties of DBS of the subthalamic nucleus (STN-DBS) on motor, neuropsychological (NPSY), and speech outcome in Parkinson. We included 48 patients (19 female, 29 male), excluding brain injuries, DBS of other targets, infections, and hardware complications. Presenting symptoms and outcomes were correlated with STN-DBS laterality/dominance, micro-electrode recordings (MER) and surgical properties at 3.8 months before STN-DBS and 16.2 months after respectively. Principle components analysis (PCA) of the pre-/post-DBS scores in the 3 outcome categories was used to design a simplified evaluation protocol.

Results: We had a homogenous group of patients in terms of symptoms' types and severity, brain dominance and gender. STN-DBS worsen frontal neuropsychological faculties and speech intelligibility, however in a rather acceptable degree in the scope of the significant improvement in the overall quality of life. In addition to the known impact of laterality, it seems that both STN-dominance and STN-neural-signal have a crucial clinical impact. Pre-DBS analyses showed that UPDRS I-III (Tremor, Rigidity/Bradykinesia, Axial Deficit), duration of PD ($10.5 \pm 4.3y$, $p=0.9$) and levodopa-equivalent drug dosage (LEDD; 1225 ± 611 , $p=0.9$) were indifferent to laterality/dominance. Mean age was lower in the bilateral STN-DBS (Bi-STN) group (54.5y) than the unilateral right-STN (Uni-Rt; 60.7y) and unilateral left-STN (Uni-Lt; 63.8y). Bi-STN patients had worse scores for activities of daily living (ADL) (Bi-STN 58, Uni-Rt 70, Uni-Lt 73, $p=0.02$) and UPDRS-IV (Bi-STN 7.30, Uni-Rt 5.38, Uni-Lt 3.69, $p=0.0037$). Voice and neuropsychology scores were normal in all groups. Following DBS, the Uni-Lt group least improved in ADL (Uni-Lt 11.7% < Uni-Rt 20.5% < Bi-STN 48.5%, $p<0.05$) and LEDD (Uni-Lt -16.9% < Uni-Rt -35% < Bi-STN -43.5%, $p<0.05$). ADL improvement was explained by the ON/OFF fluctuations (Uni-Lt -1, Uni-Rt -1.2, Bi-STN -4.2, $p<0.05$) rather than by the absolute scores (both before and after surgery). DBS was associated with a greater improvement in rigidity and bradykinesia than in tremor; the opposite result was for drugs. The ipsilateral effect of DBS was more prominent for bradykinesia than tremor. Axial deterioration was resistant to DBS (2.5, $p=0.03$). We also showed a trend of better improvement among patients undergoing DBS at earlier PD-stages. Speech intelligibility and NPSY deteriorated from normal before DBS to abnormal after Bi-STN and Uni-Lt DBS ($p<0.03$) only. Frontal-NPSY properties were more DBS-vulnerable. There was an overall unexplained increase in the use of anti-psychotic/anti-depressive drugs. DBS most significantly improved ON/OFF fluctuations will drugs improved motor symptoms. Last we PCA which yielded six clinically and mathematically independent factors: Bradykinesia-Rigidity, Tremor, Speech-intelligibility, Memory-Language, Executive functioning and Attention-Concentration. Wider STNs ($p<0.001$), higher normalized-neuronal signal ($p=0.03$), and presence of active cathodes within the β -oscillatory STN regions ($p=0.2$) were more common in patients with greater motor improvement and less speech/NPSY deterioration. As for the number of brain penetrations, we found no significant and consistent trend.

Conclusion: Within the constraints of the population size and time to survey, it seems plausible to suggest the following. ON/OFF fluctuations are affected by STN laterality and dominance and have a prominent impact on ADL. Not only STN and LEDD impacts differ (bradykinesia and rigidity for the first and tremor for the latter) but moreover Bi-STN showed the most significant effect upon ON/OFF fluctuation (compared with both unilateral groups), possibly suggesting different underlying mechanisms. Besides laterality per se clinicians should consider dominant vs non-dominant STN involvement (which might prominently impact the speech-neuropsychology profiles). On the basis of our findings, we designed an innovative and simplified evaluation protocol using representative motor, speech, and neuropsychology. We introduce a novel surgical-neurophysiological STN-score (composed of STN width, normalized neuronal signals, and β oscillations) to facilitate the decision-

making process during surgery in terms of target selection and the final location of the chronic stimulation cathode.

Movement disorders

#247

Detachment of the distal contact during removal of the DBS electrode

István Valálik (1), Péter Szloboda (1)

1. Department of Neurosurgery, St. John's Hospital, Budapest, Hungary

Submitter: Mr Valálik István (HU)

Introduction: Deep brain stimulation (DBS) is the most frequent neurosurgical procedure for movement disorders, psychiatric diseases, epilepsy and pain; therefore it has continuously been investigated. The device-related complications include infection and/or erosion, electrode disconnection or fracture, migration, and IPG malfunction. The DBS hardware is a foreign body and therefore increases the infection rate, which is a 4-12.2% per patient or a 1.5-9.7% per lead in the literature. In most of the cases partial hardware removal of the DBS system components is enough, with further maximal efforts to save the implanted leads.

In our institution we perform DBS surgeries since 1998, and the infection rate - including erosions - in our institution is 3.4%. Complete removal of the system or electrode removal was needed in 0.9 % of our cases, which is 0.6% of lead implantations. We report 2 cases when during removal of the DBS electrode the distal contact detached and remained in the brain.

Methods/results: One patient had Parkinson's disease (PD) with bilateral subthalamic DBS without micro-recording. Another patient had bilateral medial thalamic DBS for Tourette syndrome (TS) with a 4-channel micro-recording. On both sides the medial microelectrode was abandoned. In all of the targets Medtronic lead (3389 model) was implanted. For the PD patient Medtronic burr-hole cap, in TS patient StimLoc system has been used for lead fixation. No surgical complications, postoperative bleeding after surgery occurred. During the follow-up patients did not undergo MRI, physical therapy or other electromagnetic influence. Both of the patients developed delayed skin erosion with subsequent infection. Microbiologically *Staphylococcus aureus* has been identified. Repeated local and systematic antibiotic therapy with surgical debridement and lavaging provided just temporary effect. Due to recurrent infections and involvement of electrode fixation site in both cases we decided to remove the complete system. Neither clinical nor radiological signs of bone involvement, nor intracranial infection was present.

Electrodes were removed in the PD patient after 33 months, in the patient with TS 25 months after surgery. During surgery in both patients while withdrawing the left electrode, some resistance occurred. On the intraoperative fluoroscopy the detachment of the distal contact could be seen. The part of electrode with 3 contacts has been removed in PD patient, but we had to leave the distal contact with adherent wire of the electrode deeply in the electrode tract area above the subthalamic nucleus. In TS patient the phenomena was similar, but in that case we could withdraw the contact to the convexital cortical area. We did not force the total removal, as the risk of haemorrhage and infection penetration was much higher than leaving a not infected foreign body in the brain. In both cases electrode on the other side was freely removed without any complications. The isolation of the removed electrode was fragmented. Postoperative CT scanning showed in both cases a small hemorrhage near the electrode tract. We did not observe postoperative infection. The PD patient developed slight contra-lateral hemiparesis, which substantial improvement in the follow-up period.

In the presentation detailed analysis of stimulation and impedance data will be presented and potential factors causing and possibilities to predict such hardware complication will be analysed.

Conclusion: In some cases in spite of efforts to sustain the implanted DBS electrodes neurosurgeon faces with the necessity to remove them. In this cases as a technical complication the fragmentation of the electrode a precaution and careful analysing of factors have to be taken in account before removal of DBS electrodes. During surgery with electrode removal the authors suggest to use intraoperative fluoroscopic control.

#250

Multi-channel microelectrode recordings are safe and predictors of clinical outcome in Parkinson's disease treated with deep brain stimulation

Erik Johnsen (1), Bo Bergholdt (2), Niels Sunde (2), Karen Østergaard (1)
 1. Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
 2. Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark

Introduction: Deep brain stimulation (DBS) in the subthalamic nucleus (STN) is recommended treatment for advanced Parkinson's disease (PD) with motor fluctuations and severe off periods. The effect of STN DBS is comparable to an optimal dose of levodopa although the effect of stimulation is related to final contact position in the subthalamic area, documented in both clinical investigations and quantitative gait assessments. The electrode-position may be optimized with intraoperative clinical test-stimulation and perioperative imaging and/or with intraoperative microelectrode recordings (MER) mapping the target area. The first requiring the patient to leave the operation room for MRI and the latter with the risk of penetrating intra-cerebral vessels. We present our experience with multi-channel MER in STN DBS and discuss the use of it to predict clinical outcome.

Methods: All STN DBS implantations from January 2008 to December 2013 were performed using the same protocol and the same team of surgeons and neurological staff. The central part of STN was targeted on 1.5 or 3T MRI and the trajectory for insertion respected sulci, cerebral vessels, ventricle walls and STN-alignment. Multi-channel MER was used to map target area and intra-operative test-stimulation verified clinical benefit or side-effects, i.e. muscle contractures. Perioperative MRI or Computed Tomography (CT) on the next day documented lead locations and possible bleedings.

Results: Of 46 patients, 39 was treated with STN DBS using bilateral 5-channel MER; in 5 cases 3- or 4-channel MER was used due to anatomical variations on MRI. In one case, the patient refused further surgery after 5Ch MER on one side and in one patient we had a system breakdown after implanting the first electrode.

Audio-visual inspection of multi-channel MER rendered detection of dorsal-ventral, anterior-posterior and medial-lateral STN-borders possible in all patients. In 51 hemispheres (64%), all MER-channels used could define STN activity. In more than half of cases, more than one test-site was needed to optimize clinical benefit. Post-implant CT or MRI was available in all patients, and none had intracerebral bleeding. Furthermore, all electrodes followed the intended trajectory when merged with intended planning. Clinical test-stimulation predicted clinical motor-outcome at 6 months, so that all patients with clinical benefit on the table also had continued improvement after 6 months.

Conclusion: Theoretically, MER increases the risk of intra-cerebral hemorrhage during DBS surgery due to increased parenchymal penetrations. In our case-series of 451 penetrations, post-operative imaging verified no cerebral or cortical bleedings. This may relate to precise pre-operative planning based on high-resolution MRI. Furthermore, multi-channel MER were able to predict clinical motor-outcome based on 6months clinical evaluation. The safety and need of perioperative multichannel MER is much debated although our experience prove the technique to be both safe and needed in optimal DBS treatment for Parkinson's disease.

#257

Deep brain Stimulation for Tardive Dystonia in Hong Kong

Danny TM Chan (1), Cannon XL Zhu (2), Claire KY Lau (2), Vincent CT Mok (2), Jonas HM Yeug (2), Wai S Poon (2)

1. Movement Disorder Team, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China

2. Movement Disorder Team, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, Hong Kong SAR China

Introduction: Tardive Dystonia is a movement disorder caused by the use of neuroleptic medications. There is a latency of onset of days to years after exposure. The disorder affects all four limbs and the whole body. The head and neck region is the most common and severely affected area of involvement. Patients suffer from constant muscle pain and disabling limbs twitching. In its advanced stage, patients could suffer significant morbidities, such as fracture of the cervical spine and ribs, to a state of complete dependence in daily activities. Withdrawal of the offending neuroleptic medications and therapies relieving muscle clamp are the tradition treatment. However, the remission rate is low once it is developed. Surgical treatment by Deep Brain Stimulation (DBS) was reported effective in relieving the symptoms.

Results: The CUHK Neurosurgical team and Movement Disorder team have successfully treated 5 young patients with Tardive Dystonia by Deep Brain Stimulation. All five patients have suffered from severe pain and disabling dystonia a few years after exposure to the neuroleptic medications. Two of them became bedridden and needed tube feeding before DBS. Bilateral stimulating electrode were inserted to the target, the globus pallidus internus. They all showed significant improvement in 3 months. The Burke-Fahn-Marsden Dystonia Rating score (BFMDR) improved by at least 30% in the 1st week of stimulation. The swallowing function was improved after 3 months secondary to the relief of hyperextension posture of the neck. All of them showed relief of almost all the symptoms by 6 months. There was no surgical complication. They all returned to normal daily activity.

Conclusion: Bilateral chronic deep brain stimulation of globus pallidus internus is effective in the treatment of Tardive dystonia.

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Subthalamic deep brain stimulation in Parkinson's disease: the role of intraoperative microelectrode recording in short-term follow-up

Tomskiy Alexey, Gamaleya Anna, Dekopov Andrey, Bondarenko Anna, Bril Ekaterina, Salova Ekaterina, Gubareva Nataliya, Fedorova Nataliya, Buklina Svetlana, Shabalov Vladimir (1)

1. Functional Neurosurgery Group, Burdenko Neurosurgical Institute of Russian Academy of Medical Sciences - Moscow, Russia

Introduction: Maximal beneficial effect of subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson's disease (PD) could be only achieved in case of precise electrode placement. For optimization of intraoperative targeting, real-time electrophysiological mapping of basal ganglia might be used. Nevertheless, application of microelectrode recording (MER) of neuronal activity is still debatable considering related increase in surgical risks, time and material costs. There is also no clear evidence of direct advantages of MER for clinical improvement in the literature. To evaluate the impact of MER on intraoperative tactics and clinical outcome in DBS STN in patients with advanced PD.

Methods: We assessed PD patients who underwent stereotactic implantation of STN electrodes for continuous DBS in the recent years. All patients could be divided in two groups: those operated without usage of intraoperative MER (MER–, 28 patients, 56 electrodes implanted) and those with MER performed (MER+, 25 patients, 50 electrodes implanted). Except for MER, surgical technique was uniform in regard to stereotactic frame applied, imaging, planning (3D MRI navigation), and general performance. Patients operated in the first year were intentionally excluded from the study to avoid an impact of insufficient manual experience. Neurological evaluation and postoperative management were standardized. Groups were comparable in major demographic characteristics. Mean age of PD onset was 42.6(7.2) years in MER– group and 41.2(14.3) years in MER+ group; disease duration – 12.4(3.7) years and 12.8(3.8) years; age at surgery – 54.5(12.6) years and 54.6(9.7) years; Hoehn&Yahr stage – 3.5(0.6) and 3.4(0.5), respectively. We analyzed intraoperative strategy in each patient. Clinical outcome was assessed using United Parkinson Disease Scale, PDQ-39 quality of life questionnaire, Schwab&England activities of daily living scale, and changes in pharmacological therapy at months 6 and 12 postoperatively.

Results: In MER– group, central image-based trajectory was used for implantation in 96.4% of electrodes. Adjustments in depth were needed in 7.1% of electrodes. In 2 patients, correction of electrode position was performed in postoperative follow-up. Stimulation-related dysarthria was observed in 12 patients (42.9%). In MER+ group, from 1 to 5 microelectrodes were used per side, mean 2.5(0.9). Only in 62%, MRI-calculated trajectory corresponded to the optimal electrophysiologically defined track. For the final placement, medial trajectory was chosen in 26% of electrodes, lateral – in 8%, anterior – in 2%, and posterior – in 2%. Additional correction of electrode position by depth was performed in 88% of implantations. No electrode replacement was required postoperatively in MER+ group. Rate of stimulation-induced dysarthria was lower than in MER– group (by 20%, $p=0.0875$). In both groups selected, no hemorrhagic complications occurred. Preoperatively, groups did not differ significantly in clinical scoring. Following continuous DBS STN, amelioration of PD symptoms occurred in both groups. At 6- and 12-month follow-up, significant changes were observed in motor and functional scores in off-medication state (UPDRS part II and III), levodopa-induced complications rate (UPDRS IV), PDQ-39 scores, Schwab&England scores in off-state, pure levodopa dosages, and levodopa equivalent dose. In on-medication state, UPDRS III score was significantly reduced at 6-month follow-up, however, remained improved at 12-month follow-up only in MER+ patients. If compared at 12-month follow-up, in MER+ group, overall outcome in motor disability and activities of daily living appeared to be significantly better than in MER– patients: 70.2(10.5)% versus 48.7(27.9)% improvement in off-state UPDRS III, $p<0.001$; 64.5(18.0)% versus 48.8(23.0)% improvement in off-state UPDRS II, $p=0.045$; 71.8(11.3)% versus 61.5(16.3)%; in off-state Schwab&England score, $p=0.041$, respectively. Reduction in L-dopa dose and LED was more pronounced in MER+ group: 82.3(19.1)% versus 47.3(37.9)%, $p<0.001$; and 60.4(22.1)% versus 35.3(30.9)%, $p=0.008$, respectively.

Conclusion: MER seemed to improve accuracy of image-based electrode placing during stereotactic procedure. In our series of PD patients, application of MER contributed to optimization of motor and functional outcome of DBS STN in short-term follow-up. Overall impact of MER needs to be verified in larger population in long-term follow-up studies.

#264

Subthalamic deep brain stimulation in a patient with unusual presentation of Parkinson's disease

Tomskiy Alexey, Gamaleya Anna, Bondarenko Anna, Shabalov Vladimir (1)

1. Functional Neurosurgery Group, Burdenko Neurosurgical Institute of Russian Academy of Medical Sciences - Moscow, Russia

Introduction: Deep brain stimulation of subthalamic nucleus (DBS STN) is recognized worldwide as an effective and relatively safe treatment in advanced Parkinson's disease (PD). Main indications for surgical treatment in PD include the disabling motor fluctuations and levodopa-induced dyskinesias that cannot be pharmacologically managed. High dopaminergic responsiveness of parkinsonian symptoms is considered a core inclusion criterion and predictor of a good clinical outcome following DBS STN. In this regard, for application of DBS STN in parkinsonism, the diagnosis of idiopathic PD is obligatory. Although, there are some patients with idiopathic PD in whom the clinical presentation can be rather unusual. In case of simultaneous poor response to the regular dopaminergic treatment regimen, these patients might represent a significant diagnostic and therapeutic challenge. At the same time, they are not eligible for the surgical interventions according to the common CAPSIT-PD criteria. We aim to report a case of successful use of DBS STN in a female patient with unusual presentation of Parkinson's disease.

Results: The disease manifested in 2000 (at the age of 38 years) as tightness in the neck and back muscles. In 2003, mild tremor and clumsiness in the right hand appeared, followed by change in handwriting and tension in the right arm. Two years later, slight tension in the right foot added. In 2006, under the stressful conditions, axial dystonia significantly progressed and the patient developed severe trunk retroflexion during standing or walking. Right-sided bradykinesia also increased, action dystonia of the right foot appeared.

The patient was examined in several neurological clinics; however, the differential diagnosis of underlying condition was complicated. Secondary or hereditary degenerative dystonia, dopa-responsive dystonia, PD, atypical parkinsonism were considered. Brain MRI was normal. Due to the coexistence of bizarre gait disturbances and prominent depression, she was highly suspicious for the functional disorder. Levodopa test was performed, that resulted in reduction of the right hand tremor, slight reduction of bradykinesia, and slight improvement in gait. Regular intake of dopamine agonists also brought some benefit for tremor and motor function of the right arm without any effect on trunk and foot dystonia. In case of up-titration of levodopa, the beneficial effect diminished and augmentation of the right foot dystonia was observed. Other treatments, including anticholinergics, anticonvulsants, myorelaxants, and antidepressants, were unsatisfactory. Repeated botulinum toxin injections minimally reduced trunk retroflexion. Nevertheless, abnormal posturing was quite disabling; the patient used special tricks and required assistance while walking.

In 2009, almost ten years after disease onset, the left-sided parkinsonian symptoms began to appear. Transcranial sonography and DaTSCAN revealed, respectively, increased hyperechogenicity of substantia nigra and reduced striatal dopamine transporter binding. Apomorphine test performed was positive. Finally, the diagnosis of young-onset PD was confirmed. The patient was referred for functional neurosurgical evaluation.

In 2011, the patient underwent bilateral DBS STN. In the preoperative assessment, sensitivity of parkinsonian symptoms to dopaminergic therapy was less than 50% (UPDRS part III in off-medication state – 42; in on-state – 27). Medication: pramipexole 0.75 mg t.i.d., levodopa 25 mg t.i.d., lorazepam 0.5 mg t.i.d., baclofen 25 mg t.i.d. The major debilitating factor remained pharmacologically refractory axial and right leg dystonia (BFMDRS – 14; PDQ-39 – 153).

After 3 years following continuous DBS STN, significant reduction of all parkinsonian symptoms occurred (60% improvement in off-state UPDRS III – 17; UPDRS III in on-state – 10). Dystonia relieved completely (BFMDRS – 0; PDQ-39 – 67). Levodopa equivalent dose (LED) was unchanged, although, the pure levodopa dosage decreased. Medication: pramipexole ER 3 mg once a day, levodopa 25 mg seldom if needed.

Conclusion: DBS STN presents an effective treatment for PD, even when complicated with severe dystonia unresponsive to dopaminergic therapy. Currently available diagnostic techniques (neurosonography, DAT-SPECT) improve the diagnosis in patients with unusual presentation of PD,

contribute to selection of the optimal target for DBS, and allow reaching perfect results of surgical treatment.

Movement disorders

#265

Extended Programming with VERCISE Neurostimulator in the VANTAGE Multi-Site Clinical Trial

Lars Timmermann¹, François Alesch², Thomas Brücke³, Esther Suarez San Martin⁴, Mauro Porta⁵, Alan Whone⁶, Marc Verin⁷, Fernando Seijo⁴, Domenico Servello⁵, Steven Gill⁶, Claire Haegelen⁷, Mohammad Maarouf¹, G. Karl Steinke⁸, Stephen Carcier⁸, Lilly Chen⁸

1. Universitätsklinikum Köln 2. Medical University of Vienna 3. Wilhelminenspital 4. Hospital Central de Asturias 5. Istituto Galeazzi IRCCS Milano 6. Frenchay Hospital 7. CHU de Rennes-Ponchaillou 8. Boston Scientific Neuromodulation

Introduction: Historically, DBS systems have delivered stimulation using a single electrical source. The Vercise DBS system provides an independent current source for each of its 16 contacts, which allows control of current on more than one contact of either polarity on a lead (Current Steering), a feature which could potentially enhance efficacy (Butson 2008). The Vercise system also provides an expanded range of programming parameters (pulse width, rate, multiple rates), which may result in additional clinical benefit. We sought to characterize the extent of extended programming use in the VANTAGE trial, and examined whether trends were observable in specific utilization patterns.

Methods: Forty (40) patients with idiopathic Parkinson's disease were implanted bilaterally with the Boston Scientific Neuromodulation (BSN) DBS system (Vercise). Patients waited 2-18 days before being activated, and follow up occurred at 12, 21, 26, and 52 weeks post-implantation. Exploratory data analysis was performed to characterize the utilization of extended programming features in the VANTAGE trial. Data visualization was used to examine for trends of differential utilization patterns among different patient subgroups.

Results: Full programming parameters is available from activation through 52 weeks (1 year) post-implantation. Details of programming parameters, including use of current steering, pulse widths, and rates will be presented. Changing utilization patterns over time will be presented across multiple patient subgroups.

Conclusion: DBS treatment with the Vercise system allowed for expanded programming options the VANTAGE study. Analysis of patients programmed with new features unique to the Vercise system (current steering, multiple-rate, new pulsewidths, etc.) may inform further studies to evaluate the relationship between extended programming and outcomes.

#266

Deep Brain Stimulation at short pulse width results in superior therapeutic windows for treatment of Parkinson's Disease: a randomized, controlled, double-blind neurostimulation trial (CUSTOM-DBS).

Jens Volkmann¹, Frank Steigerwald¹, Martin Reich¹, Anna-Dalal Sawalhe¹, Lars Timmermann², Michael Barbe², Andrea A. Kühn³, Julius Hübl³, Alfons Schnitzler⁴, Stefan Jun Groiss⁴, Alexia Moldovan⁴, Karl Steinke⁵, Sherry Lin⁵, Ljubomir Manola⁵, Stephen Carcier⁵

¹Universitätsklinikum Würzburg; ²Universitätsklinikum Köln; ³Charité, University Medicine Berlin; ⁴Universitätsklinikum Düsseldorf; ⁵Boston Scientific Neuromodulation, Valencia, CA

Introduction: The primary objective of this study was to demonstrate in patients with Parkinson's disease (PD) that deep brain stimulation (DBS) at short pulse width (30 μ s) results in larger therapeutic windows without compromising efficacy, when compared to DBS at conventional pulse width (60 μ s). Therapeutic window was defined as the difference in amplitude of first stimulation-induced side effects (side effect threshold) and amplitude of the lowest setting allowing full rigidity control (efficacy threshold). Efficacy was assessed using UPDRS III score with a non-inferiority margin of 5 points between the short and conventional pulse widths.

Previous researchers have proposed that DBS at short pulse width may decrease the risk of stimulation-related side effects by expanding the therapeutic window. However, expectation can lead to placebo effects in PD, and there remains a need to test DBS programming recommendations in a double-blind condition. In this study we performed double-blind assessments of acute stimulation challenges with different parameter combinations, in order to determine which settings reduce the risk of side effects without sacrificing any significant therapeutic benefit.

Methods: Fifteen (15) PD patients implanted with Boston Scientific's Vercise DBS system for more than 3 months were programmed using test pulse widths of 30 μ s and control pulse widths at 60 μ s delivered via single best therapeutic contact. Thresholds for efficacy and side effects as well as UPDRS III were measured in the *meds off* condition at test and control settings. For all assessments, subject and evaluating neurologist were blinded to the pulse width setting, and statistical analyses were pre-defined. The primary outcome was the width of the therapeutic window (in mA) for the two stimulation conditions.

Results: Stimulation at 30 μ s pulse width resulted in a significantly larger therapeutic window when compared to stimulation at conventional pulse width of 60 μ s ($p = .0009$; paired t-test). Efficacy, as measured by UPDRS III score, of short pulse width programming was found to be non-inferior (margin = 5 points, the established minimal clinically important change for UPDRS-III (Schrag et al, 2006)) when compared to conventional programming ($p = .00008$; paired t-test). Mean efficacy threshold was at a higher current amplitude for short pulse width settings, but the mean total charge delivered per pulse was lower, suggesting that short pulse width settings may require less electrical energy to reach the efficacy threshold (Mean amplitude = 3.05 mA at 30 μ s, 2.31 mA at 60 μ s; mean charge per pulse = 91.5 nC/pulse at 30 μ s, 138.6 nC/pulse at 60 μ s).

Conclusion: This study is the first double-blind assessment comparing stimulation at a pulse width shorter than 60 μ s to conventional DBS settings at 60 μ s pulse width. The larger therapeutic window at 30 μ s suggests that shorter pulse widths may be advantageous for avoiding stimulation-related side effects. This larger therapeutic window was achieved while maintaining efficacy as measured by a non-inferiority comparison of UPDRS III. Importantly, the short pulse width setting required less electrical energy delivered to achieve an efficacy threshold, suggesting there may also be energy efficiency advantages to those settings.

#277

VANTAGE trial: Twelve month (12 mo.) follow up of a prospective, multi-center trial evaluating Deep Brain Stimulation with a new multiple-source, constant-current rechargeable system (Vercise™) in Parkinson's disease

Lars Timmermann¹, Roshini Jain², Lilly Chen², Thomas Brücke³, Fernando Seijo⁴, Esther Suarez San Martin⁴, Claire Haegelen⁵, Marc Verin⁵, Mohammed Maarouf, Michael T. Barbe¹, Steve Gill⁶, Alan Whone⁶, Mauro Porta⁷, Domenico Servello⁷, François Alesch⁸

1. Univ. Hospital, Cologne, Germany 2. Boston Scientific Neuromodulation, Valencia, CA. 3. Wilhelminenspital Vienna, Austria 4. Hosp. Central de Asturias Oviedo, Spain 5. CHU de Rennes-Pontchaillou Rennes, France 6. Frenchay Hosp., Bristol, UK 7. Galeazzi Hosp., Milan, Italy 8. Medical Univ. of Vienna, Vienna, Austria

Introduction: The VANTAGE study assessed motor improvement in moderate-to-severe Parkinson's disease (PD) up to 12 months following bilateral subthalamic nucleus deep brain stimulation (DBS) using an implantable, rechargeable, multiple-source, 8-contact, constant-current DBS System, Boston Scientific's Vercise System.

Several randomized controlled trials (Deuschl 2006, Weaver 2009, Okun 2012) have demonstrated that DBS is an effective treatment for patients with Parkinson's disease. Motor improvement following DBS is sustained up to 10 years (Castrioto 2011). We sought to characterize the benefit of STN-DBS for PD patients using a recently-approved multiple-source, constant-current system that permits a well-defined distribution of applied current. We report here the 12-month results of the first clinical trial for multiple independent current control (MICC) DBS in the treatment of Parkinson's disease.

Methods: VANTAGE is a monitored, prospective, multi-center, non-randomized, open-label interventional trial, sponsored by Boston Scientific Corporation. 40 subjects with idiopathic Parkinson's disease (PD) were implanted bilaterally in the subthalamic nucleus (STN). Subjects were followed at 3, 6 and 12 months post lead placement. Motor improvement was evaluated using UPDRS III scores in stim ON/meds OFF as compared with pre-operative scores. Other assessments such as CAPSIT motor tests, Tremor Rating Scale, Dyskinesia Rating Scale, PDQ-39, SF-36, Schwab and England, and resource utilization were administered. Patient motor diaries were collected over 3 days. Adverse events were recorded.

Results: A highly significant improvement of 62% in UPDRS III scores at 12 months post implant in stim on/meds off condition was reported. Medication usage, as calculated using levodopa equivalents, was reduced by 53% at 6 months and 58% at 12 months compared to pre-operative usage. Highly significant improvement was also demonstrated in overall quality of life as reported using PDQ-39, Schwab and England and motor diaries.

Conclusion: Highly significant motor improvement, as evaluated using UPDRS III, was demonstrated at 6 months that was further sustained up to 12 months post lead placement in 40 subjects implanted with Vercise system. Subjects overall quality of life also improved significantly. The VANTAGE trial is the first reported trial of a multiple-source, constant-current rechargeable system (Boston Scientific's Vercise System) in PD up to 12 months.

2.2 Psychiatric Disorders

#39

DBS in Major Depressive Disorder

DOMENICO SERVELLO (1), EDVIN ZEKAJ (1), CLAUDIA MENGHETTI (1), GIOVANNI BROGGI (1), MAURO PORTA (1)
1. *NEUROSURGERY, IRRCS GALEAZZI MILAN, MILAN, Italy*

Introduction: Depression is one of the leading causes of disabilities in the developed countries.

Methods: we report two male patients affected with treatment resistant major depressive disorder who underwent DBS of the Nucleus Accumbens (NAcc).

Results: In the follow-up at 3, 6, 12 and 24 months one patient presented an improvement of disorder while the other one a poor response was observed.

Conclusion: treatment resistant depression is a challenging disorder, in carefully selected cases DBS might represent a last resort.

#113

Deep Brain Stimulation for the treatment of Refractory Cocaine Dependence: Case report with 2 years follow-up

Antonio Gonçalves-Ferreira (1), Alexandre Rainha-Campos (1), Frederico Simões Couto (2), Lia Lucas Neto (3), Diogo Gonçalves Ferreira (2), Joana Teixeira (4), Lucilia Salgado (5), Martin Lauterbach (6), Maria Ceu Rueff (7), Helena Raposo (8), Rui Sequeira

1. Neurosurgery, University Hospital Santa Maria, Lisbon, Portugal

2. Psychiatry, University Hospital Santa Maria, Lisbon, Portugal

3. Neurological Imaging, University Hospital Santa Maria, Lisbon, Portugal

4. Psychiatry, University Hospital Santa Maria, Lisbon, Portugal

5. PET, Instituto Portugues Oncologia, Lisbon, Portugal

6. MRI, Centro Ressonancia Magnetica, Lisbon, Portugal

7. Faculty of Law, Faculty of Law, Lisbon, Portugal

8. Centro Atendimento Toxicodependentes, Centro Atendimento Toxicodependentes, Barreiro, Portugal

9. Centro de Atendimento de Toxicodependentes, Centro de Atendimento de Toxicodependentes, Barreira, Portugal

Introduction: The neuronal basis of addiction comprehend the limbic system and the brain rewarding circuits, namely the ventral striatum nucleus accumbens (Acc), the bed nucleus of stria terminalis (NST) and anterior limb of the Internal Capsule (IC) the middle forebrain bundle (MFB). Preliminary data from other groups point to some degree of clinical efficacy of Acc DBS in alcohol and heroin refractory dependence, but it has never been shown an effect in cocaine. Moreover doubts have been raised about the best target to use and the exact localization of Acc. Our group has studied the precise Acc localization and its intimate neighborhood. The main objective of this study is therefore to evaluate the clinical efficacy of DBS on Acc/NST/IC in the treatment of cocaine refractory dependence.

Methods: One male 36 year old man with a 16 years history of refractory cocaine dependence (DSM IV 304.20) was the first patient admitted for surgery of a larger study approved by the local Ethics Committee. The refractoriness was confirmed and the surgical indication approved by two independent psychiatrists nominated by the National Council for Mental Health, after an appropriate informed consent was signed. An electrode (3387 Medtronic®) was implanted on each side under local anesthesia through an intraparenchymous trajectory designed to reach all the targets: contact 0 was 3mm underneath the AC, 5.5mm apart from the midline, within the posterior Acc according to our anatomical data; contact 1 was in the antero-lateral limit of NST at the level of the anterior commissure (AC) 6.5mm apart from the midline; contact 2 was 3 mm above the AC, in the anterior IC; contact 3 was 6mm above the AC, also in the anterior IC. The cortical entry points were in the posterior F2 gyrus. The electrodes were connected subcutaneously to an Activa PC® pulse generator. Monopolar stimulation was performed at each contact during the operation. No operative morbidity was registered. The post-operative DBS started 5 days after the operation. the initial parameters were: active contacts 0-1-2 with 130hz frequency, 150µs pulse width and 2.0 volts amplitude; the definite ones were: active contacts 0-1 with 150hz frequency, 150µs pulse width and 2.5-3.0(left) 3.0-4.0(right)volts amplitude.

Results: After 24 months of DBS, including 6 months of randomized double blind stimulation, the results are: Primary variables: The number of weeks free of consumption changed from 9/22 (40%) before surgery (BS) to 16/20 (80%) 4 months and 34/50 (70%) 2 years after surgery (AS); the percentage of negative urine analysis followed the same range. Secondary variables (BS and 12 months AS): The cocaine craving score (VAS: 0-10) changed from 3.4 BS to 0 AS;

The desire and intension to use (DDQ: 0-7) changed from 3 to 0 AS;

The negative reinforcement of cocaine use (DDQ: 0-4) changed from 3 BS to 0 AS;

The YBOCS (0-40) changed from 14 BS to 4 AS;

The CGI S (1-7) changed from 5 BS to 1 AS.

Other secondary variables changed in the same range.

Safety and tolerance: Occasional whole body flush with sweating and increase temperature (contact 0 left stimulation); Occasional metallic taste and contra lateral hemi-smile (contact 1 stimulation);

Transitory diminished libido during the post-operative adjustment period (high voltage);

Transitory weight gain.

Conclusion: DBS was useful and safe in the treatment of this case of refractory cocaine addiction. These preliminary results compel us to study other similar cases to reach more conclusive results.

#135

Vagus Nerve Stimulation (VNS) for the treatment of mood disorders. Revisiting the past?

Christine Matthews (1), Serenella Tolomeo (1), Keith Matthews (1)
1. Division of Neuroscience, University of Dundee, Dundee, United Kingdom

Introduction: Vagus Nerve Stimulation (VNS) is currently offered as a treatment for mood disorders, particularly Major Depression. A mood elevating effect was first noted in patients receiving VNS therapy for the treatment of epilepsy. Consequently the manufacturer (Cyberonics Inc) initiated a series of trials to examine the utility of VNS in Major Depression. A body of literature describes the conduct and outcomes of these trials. Recent open case series data suggests that VNS may be associated with significant clinical improvement for around one third of patients with highly treatment refractory and chronic Major Depression.

In a recent Health Technology Assessment of VNS for Depression, 18 relevant publications were identified by NICE (UK National Institute for Health Care and Clinical Excellence, 2009). They concluded that a published total of 1251 VNS procedures had been completed. Of these, between 27 and 58% of patients were found to have a satisfactory outcome (defined as > 50% reduction in the baseline Hamilton Depression Rating Scale (HDRS) score). However, a more recent meta-analysis by Berry et al (2013) argued that only 1035 patients received VNS through participation in the Cyberonics-sponsored studies. This represents a substantial (-17%) discrepancy from the figures derived by NICE. We therefore sought to identify accurately the numbers of patients reported and to estimate treatment outcomes.

Methods: We used the search terms “VNS” and (“vag*” AND “stimulat*”) with each of “psychiat*”, “mental” and “depress*” to identify the literature from 2000. We also employed terms to capture 13 other psychiatric diagnostic criteria. Searches were conducted systematically and were not restricted to English. However no attempt was made to conduct specific searches in other languages. After initial screening of titles and abstracts; case reports, trials and follow up studies were retrieved. Studies which gave wider, contextual information were retained for background information and were augmented using material drawn from relevant websites (eg Cyberonics, ClinicalTrials.gov, MAUDE). By examining studies within this context and by removing papers where repeat reporting was evident (or likely), a more conservative estimate of the total population was made. Outcomes were then considered within this framework.

Results: Of 1627 papers retrieved, 758 were relevant to the topic. After hand searching for further papers, duplicates were removed. Papers were then reviewed at abstract level and 123 full papers examined in detail. Relevant information was available in 73 papers. When broken down by unique trial identifier, 14 of these papers provided data for 60 patients implanted in D01, 16 papers for data on 235 patients implanted in D02 and 15 for 74 patients implanted in D03. A further 4 papers were found describing 331 patients implanted for D21. A total of 24 papers described a maximum of 76 implants that could not be directly attributed to a Cyberonics-sponsored study. A significant proportion of these described case reports (81%).

While the review by Berry et al included 335 patients participating in D23, this was an observational study and included patients from D21. Therefore, from this information and by reviewing study inclusion and exclusion criteria, we can only be confident that 780 patients have been implanted with VNS. This is significantly lower than the number derived by either NICE (62%) or Berry et al (75%). Both reviews appear to have double counted participants.

Conclusion: VNS may have benefits in a treatment resistant population of patients with chronic major depression. However, the literature is confusing with apparent multiple reporting. The actual number of procedures conducted appears to be considerably lower than previous estimates. Outcome data is available for only a proportion of these. Despite an extensive literature, it is difficult to estimate reliably the safety and effectiveness of VNS as a treatment for Major Depression.

#137

Anterior Cingulotomy for Major Depression does not impair Stroop task performance but Depression Severity Does.

Serenella Tolomeo (1), Ines Jentzsch (2), Christine Matthews (1), David Christmas (1), J. Douglas Steele (1), Keith Matthews (1)

1. Division of Neuroscience, University of Dundee, Dundee, United Kingdom

2. Psychology, University of St Andrews, St Andrews, United Kingdom

Introduction: Neuropsychological impairment on the Stroop task – a classic neuropsychological task measuring the effect of interference on attention and reaction time - has been consistently demonstrated in patients with depression (Epp, 2012). Extensive anterior cingulate cortex damage in non-depressed humans is also associated with impairments on the Stroop task (Ochsner, 2001). Anterior cingulotomy (ACING) is a neurosurgical therapy for treatment-resistant depression (TRD) and involves the creation of bilateral lesions in the dorsal anterior cingulate cortex. It is not known whether patients who receive this treatment show impairments on Stroop performance. We therefore tested the hypothesis that mood and ACING would induce deficits (increased errors and slower responses) on the Stroop task.

Methods: Brain structure and neuropsychological functioning were investigated in 15 patients with a diagnosis of TRD who received ACING, 20 matched TRD patients who had not received ACING (TRD), and 20 healthy, never-depressed controls (all matched for age, IQ and gender). T1 weighted Magnetic Resonance Images were acquired.

Results: Both ACING and TRD groups showed performance deficits when compared with controls on the emotional and classical Stroop tasks. However, the ACING group did not show greater performance deficits than the TRD group. The number of correct responses and errors were highly correlated with clinical ratings of depression severity in both ACING and TRD groups. Patients who had received ACING and made a good recovery following surgery performed similarly to controls. The Stroop reaction time effect, which involves slowing on incongruent trials, correlated with white matter reductions in the anterior cingulate cortex. Increased reaction times strongly correlated with white matter reductions in the amygdala/hippocampal complex, a region implicated in TRD, but presumed unaffected by ACING.

Conclusion: This study supports the interpretation that ACING does not impair Stroop performance, but that depression (TRD) does. This may be because the ACING procedure produces smaller, discrete lesions compared to those previously described in the literature as associated with Stroop task impairment.

#151

Deep brain stimulation in pathological aggression – a case report

Marek Harat (1), Marcin Rudaś (1), Paweł Sokal (1), Piotr Zieliński (1)
1. Neurosurgery, Military Research Hospital, Bydgoszcz, Poland

Introduction: We present a case of deep brain stimulation in a female patient with extremely severe aggression refractory to conservative treatment. The target has been designated bilaterally in the posterior-medial part of the hypothalamus and in the absence of improvement bilaterally in the nucleus accumbens.

Methods: Initially, we implanted two electrodes to the postero-medial hypothalamus, based on the experiences of other centers. We obtained proper consent of the Bioethics Committee. In the early postoperative period, we observed improvement in the range of 50-90 % in terms of quantity and quality of attacks of aggression. However, after about 3-4 weeks bouts of aggression started to return to preoperative frequency and strength. Despite the changes in the stimulation parameters, including polarity, frequency (high / low) there was no improvement. For this reason, based on the experience with surgery in patients with obsessive-compulsive disorder, Tourette syndrome, morbid obesity (improving mood in these patients) we decided to place the electrodes into the nucleus accumbens.

Results: After several months of follow-up, the patient has no aggressive disorder, can sleep 8 hour during the night, participates in daily family activities

Conclusion: Although the stimulation of the posterior - medial hypothalamus did not bring long-term benefits, a combination of bilateral stimulation of the nucleus accumbens practically set the patient free from aggressive behaviour. It significantly improved the quality of her life, family and social relationships. We did not observe at the same time any side effects of stimulation.

#191

Deep brain stimulation in kleefstra syndrome

David Segar (1), Yosef Chodakiewitz (1), Radmehr Torabi (2), G. Rees Cosgrove (2)

1. Neurosurgery, Warren Alpert Medical School of Brown University, Providence, United States

2. Neurosurgery, Rhode Island Hospital; The Warren Alpert Medical School of Brown University, Providence, United States

Introduction: Deep brain stimulation (DBS) has been reported to have beneficial effects in severe, treatment-refractory cases of obsessive-compulsive disorder (OCD) and Tourette syndrome. In this report, we present a case of bilateral ventral capsule/ventral striatum (VC/VS) DBS providing significant symptomatic and functional improvement in a patient diagnosed with Kleefstra syndrome. This syndrome, characterized by a phenotype of childhood hypotonia, intellectual disability, and distinctive facial features, is often accompanied by myriad psychiatric and behavioral disorders. This report describes the first case in which DBS was used to treat the neuropsychiatric symptoms of Kleefstra syndrome.

Methods: A 24-year-old female patient with hypotonia at birth, developmental delay and diagnoses of autism spectrum disorder, OCD, and Tourette syndrome refractory to medical management underwent bilateral placement of VC/VS DBS with clinical improvement. DBS malfunction/failure required replacement of the bilateral leads. Her clinical course was monitored while on and off stimulation.

Results: Upon undergoing initial VC/VS DBS, medical providers and family observed ensuing improvement in the patient's compulsive behaviors, coprolalia, speech, social interaction and general functioning. Subsequent clinical regression prompted investigation, which revealed that one DBS lead had fractured and the other had migrated from its original location. Both leads were explanted and replaced in their original locations with restoration of functional improvement. Genetic testing later demonstrated a 9q34.3 microdeletion affecting the euchromatin-histone-lysine-N-methyltransferase-1 (EHMT1) gene, and the patient was diagnosed with Kleefstra syndrome. Although patients with this syndrome may demonstrate a regressive course,(4) this patient continues to function substantially above her baseline more than two years after DBS replacement. Occasional worsening of symptoms during this time has largely been reversed or improved with voltage and contact adjustments. Notable improvements in communication and social interaction have resulted in significant qualitative benefits to the patient and her family.

Conclusion: The symptomatic and functional improvement observed in this case of VC/VS DBS for Kleefstra Syndrome suggests a possible novel application of DBS.

The decline in function following electrode malfunction and subsequent recovery following correct re-implantation implicates DBS as the likely causal factor for the patient's improvement. This correlation, together with the longevity of ongoing benefits to the patient, suggests a possible therapeutic role for DBS in patients with this rare disease.

#209

DBS of the nucleus basalis of Meynert in Alzheimer's disease: results of a pilot study and its implications for the start of a larger randomized controlled trial.

Pablo Andrade (1), Doris Lenartz (2), Rowshanak Hashemiyoon (2), Jens Kuhn (3), Veerle Visser-Vandewalle (2)

1. Department of Neurosurgery, University of Cologne, Cologne, Germany

2. Department of Stereotactic and Functional Neurosurgery, University of Cologne, Cologne, Germany

3. Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany

Introduction: The effectiveness of deep brain stimulation (DBS) in substantially reducing the refractory symptoms of movement disorders, such as Parkinson's disease, has encouraged the investigation of this therapeutic application to other treatment-resistant disorders. Alzheimer's disease (AD) represents one of the most challenging neurodegenerative diseases in our society, accounting for 60% of all dementia-related disorders worldwide. Despite this, no effective treatments are available to arrest the progression of this disease. Recently, pre-clinical and clinical studies have indicated that DBS may improve the decline of cognitive function in those afflicted with AD.

While optimal target selection is still under investigation, two deep brain structures have been the focus of consideration because of their potential role in AD-associated impairment. These are the fornix and the nucleus basalis of Meynert (NBM). In addition to acetylcholine being an essential neurotransmitter for attention and memory function, the atrophy and loss of the cholinergic cells of the NBM in particular are directly implicated in AD pathology and its associated cognitive impairment. Moreover, this large cholinergic cell population has extensive cortical connectivity, thus allowing for more pervasive and long-lasting therapeutic effects. While this makes the NBM a particularly attractive target, safely accessing the appropriate areas in this diffuse region for suitable activation has not been properly addressed.

Methods: The pilot study for this target included a randomized double-blind phase for a period of one month with 2 weeks ON and 2 weeks OFF stimulation (or vice versa), followed by an open continuous stimulation period of 11 months (Kuhn J et al., 2014). While the results of this study showed some moderate improvement, there was a high variability in electrode locations.

While drawing on the technical issues of this pilot study, we will further address the challenges of accessing the NBM by modeling the viability of various trajectories for electrode placement using continuous and maximum probability maps. Finally, we will quantify the therapeutic effect of DBS using predictive pattern analysis to determine deviation from each individual's unique degeneration path. We hypothesize that the stimulation of cholinergic neurons of the NBM can contribute to the stabilization or improvement of cognitive functions in AD patients.

#223

Deep brain stimulation for depression: scientific and ethical issues

Philip Mosley (1), Rodney Marsh (1)

1. Neuropsychiatry, Asia-Pacific Centre for Neuromodulation, Brisbane, Australia

Introduction: Depression is a common, burdensome condition that reduces quality of life, leads to social role impairment and has serious economic consequences. For many sufferers, residual symptoms persist following treatment with conventional therapies. In the most severe cases, patients may fail to respond to a combination of biological and psychological treatments, leading to profound disability. Deep brain stimulation (DBS) is an emerging intervention for these treatment-resistant patients, but remains in the experimental phase. Open trials have consistently shown a sustained clinical response to chronic stimulation in the majority of subjects, which is remarkable given the chronicity and treatment-refractoriness of the sample. However, two recent randomised, double-blind, placebo-controlled trials have failed to replicate these results. Our aim in this paper was to generate potential explanations for these discrepant findings. We also examine ethical issues, with a focus on psychiatric adverse events, expanding on the consensus reached in the literature to date.

Methods: We conducted a systematic review of the published open studies and compared them with available data from the recent placebo-controlled trials. We supplemented our investigation with a hand search of the Medline database for publications by authors in the major groups undertaking DBS for mood disorders. We added our experience from the Asia-Pacific Centre for Neuromodulation, the largest Australian DBS centre for movement disorders.

Results: Scientific Issues - We considered a placebo effect that overestimated the response in open trials and examined factors relating to anatomical targeting and DBS programming in the more recent controlled trials. However, the most important issues are likely to be the pattern of network activation induced by stimulation, the identification of appropriate candidates and the duration of active stimulation in the crossover protocol. We suggest a greater focus on melancholia and question the selection of patients who have failed to respond to electroconvulsive therapy.

Ethical Issues - We discuss the high rate of suicidal behaviour in this sample, considering the effects of DBS on impulsivity in the movement disorder population, as well as nonspecific psychological variables that may disrupt postoperative adaptation. We consider the management of risk in those with treatment-resistant depression and risk factors for suicide, concluding that it may nevertheless be acceptable to offer DBS, providing there is established evidence of benefit over placebo.

Conclusion: We anticipate methodological refinements that will permit future randomised, controlled trials in this field.

#242

Deep brain stimulation in five patients with obsessive compulsive disorder

István Valálik (1), András Harsányi (2), Katalin Csigó (2), Attila Németh (2)

1. Department of Neurosurgery, St. John's Hospital, Budapest, Hungary

2. Department of Psychiatry II., Nyírő Gyula Hospital - National Institute of Psychiatry and Addictions, Budapest, Hungary

Introduction: Deep brain stimulation (DBS) appears to be a relatively effective treatment for patients with severe obsessive compulsive disorder (OCD) who have not responded to other treatments. Medication and/or psychotherapeutic help such as cognitive behavioral therapy does not help between 20-30% of patients relieve their symptoms.

Methods: Five patients with therapy-resistant OCD were selected for surgery by our research group. The patient selection was based on published and accepted inclusion and exclusion criteria. The patients' score according to the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was between 32 and 39. Prior to the surgery frameless MR imaging was performed including diffusion-tensor MRI protocol. Deterministic and probabilistic tractography using Slicer and FSL software packages and running on Linux operating system were used to visualise the tentative target region connectivity as pre-processing for surgical planning. For stereotactic planning we used home-developed Vister-3D planning software with CT-MR image co-registration. In the first 2 cases the anterior limb of the internal capsule, whereas in the following 3 patients the nucleus accumbens was selected as a target for lead implantation. In 4 cases model 3387 electrodes, while in 1 case model 3361 electrodes (Medtronic Inc.) were implanted bilaterally. Intra-operatively a 5-channel micro-electrode recording was applied. The electrode position was controlled with postoperative CT and co-registered to preoperative MRI and tractography.

Results: The Y-BOCS score after surgery in all patients showed a significant improvement. In spite of the improvement in OCD symptoms, 1 patient died by suicide 3 months after surgery. The follow-up period in rest of the patients lasted from 12 to 96 months.

In 3 of the patients battery replacement was needed, and a rechargeable pulse generator (Activa RC) was implanted. No surgical complications were observed. In 1 case slight stimulation-related complications were observed, but later they were eliminated after the refinement of the stimulation parameters. 1 patient, who had co-morbid Marfan-syndrome developed temporary superficial skin erosion above the pulse generator from the heating effect of recharging. The problem was successfully treated with local treatment and changing the charging pattern with applying charging of a higher frequency but shorter duration.

Conclusion: DBS is an effective treatment option for severe drug resistant OCD cases. Tractography can be a promising tool in surgical planning. There was also a significant improvement in their overall ability to return to normal family life, engage in new relationships or go back to work. In a multidisciplinary assessment and follow-up special attention has to be paid to the selection of candidates for surgery, especially in patients with previous suicide attempts. Postoperative depression should be carefully assessed and recognized in time and treated in order to prevent suicide attempt in patients with this comorbidity.

#248

DBS in severe addiction: first experiences with stimulating the nucleus accumbens and review of the literature

Jens Kuhn (1), Doris Lenartz (2), Rowshanak Hashemiyoony (2), Veerle Visser-Vandewalle (2)

1. Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany

2. Department of Stereotactic and Functional Neurosurgery, University of Cologne, Cologne, Germany

Approximately one-quarter of the mortality rate in the Western world is due to psychotropic substances. Thus, the most frequently occurring psychiatric disorders are substance-related addictions. A prevailing theory for the formation and maintenance of addiction is a substance-induced dysfunction of the brain's reward system. Nevertheless, pharmacological, psychological and socially therapeutic interventions aimed at modulating dysregulated networks are still grossly insufficient, resulting in relapse rates of at least 50-70% after one year.

Deep brain stimulation (DBS) has proved to be a powerful tool for modulating dysregulated networks. With successful application and approval for several neurological disorders, DBS has been recently researched as a viable therapeutic option for substance-related addiction in both animal and human studies. As with other brain disorders to which DBS therapy has been extended, the question of target selection is an important issue.

As part of the ventral striatum, the nucleus accumbens (NA) plays a key role in reward-seeking behavior as well as the motivated actions that lead to reward; thus, it is designated a limbic-motor interface. In the early stages of addiction, it is part of the positive reinforcement phase. During later withdrawal, it can be associated with the negative reinforcement that drives goal-directed behavior. Its extensive afferent and efferent connections - which include the amygdala, hippocampus, prefrontal cortex, thalamus, globus pallidus, and midbrain dopamine structures - uniquely position it as a central structure in the addiction cycle.

The first promising case reports of DBS in the NA of humans with intractable addiction have recently been published with positive results. These are supported by animal investigations mimicking addiction to various psychotropic substances such as ethanol, cocaine, and morphine. In contrast to these are findings of the effects of DBS on a second target - the subthalamic nucleus - in both humans and animals. There are also a small number of preclinical studies exploring other targets such as the dorsal striatum, hypothalamus, lateral habenula, and medial prefrontal cortex.

This presentation is intended to point out the current state of knowledge on DBS in substance dependence with a special focus on our own experiences with the nucleus accumbens.

2.3 Epilepsy

#85

Efficacy of Vagus Nerve Stimulation (VNS) for treatment of refractive epilepsy in the pediatric population: our institutional series

Claudio Ruggiero (1), Sibilla Salvia (2), Giuseppe Mirone (3), Pietro Spennato (1), Giuliana Di Martino (1), Salvatore Buono (4), Giuseppe Cinalli (1)

1. Neurosurgery, AORN Santobono-Pausilipon, Naples, Italy

2. Neurology, AORN Santobono-Pausilipon, Naples, Italy

3. neurosurgery, AORN Santobono-Pausilipon, Naples, Italy

4. Neurology, AORN Santobono-Pausilipon, Naples, Italy

Introduction: Pediatric epilepsy is one of the most prevalent neurological disorders of the childhood. Notably, at least 30-40 % of these patients are treatment-resistant. Since 2010, our Unit of Epilepsy Surgery recommends vagus nerve stimulation (VNS) as a palliative treatment for patients who are not candidates for functional surgery. In this study, we have reviewed our institutional series to assess the impact of VNS on seizures and quality of life of pediatric epileptic patients.

Methods: We retrospectively reviewed the medical records of 15 patients with treatment-resistant epilepsy who received surgical implantation of the VNS device in our Unit between 2010 and 2013. Quality of life of patients was monitored by means of the clinical examination and periodical interview.

Results: Complete follow-up data was obtained for all 15 patients (8 boys and 7 girls), and median follow-up was 18 months (range 6-48 months). Reduction of seizure frequency occurred in all patients after 12 months. 90% of families observed a positive or very positive impact on the quality of life of patients. Technical and functional complications of the VNS stimulator occurred in two patients.

Conclusion: The VNS is a safe, generally well tolerated, palliative treatment for pediatric patients with treatment-resistant epilepsy that shows a positive impact on the quality of life of patients and their families.

#97

Vagal Nerve Stimulation in metabolic encephalopathies: report of two cases

Andrea Trezza (1), Daniele Grioni (2), Leonardo Fiori (1), Carlo Giussani (3), Clarissa Cavandoli (1), Andrea Landi (1), Erik Sganzerla (1)

1. Neurosurgery, San Gerardo Hospital, Monza, Italy

2. Paediatric Neurology, San Gerardo Hospital, Monza, Italy

3. Neurosurgery, San Gerardo Hospital, Monza, Italy

Introduction: Vagal Nerve Stimulation (VNS) is considered to be effective in some cases of drug resistant epilepsy not suitable for resective surgery. Metabolic encephalopathy are frequently associated with intractable epilepsy, usually featuring as generalized fits or myoclonic spasms; in our experience, as reported from different Authors, VNS seems to be of particular efficacy in myoclonic epilepsy in children; moreover, few reports deal with the results of VNS in patients with epileptic encephalopathy in metabolic disease. No report concerns with GA II. Tsao reported good results treating with VNS two NKH drug resistant patients, achieving seizure control and reducing at the same time the number of drugs. We report our experience in treating refractory epilepsy with VNS in two patients affected by inborn error of metabolism.

Methods: Among the patients followed by our Metabolic Disease Centre, two patients were selected for drug resistant epilepsy. The first patient was a 23 years-old patient affected by glutaric aciduria (GA) type 2, the other one was a 16-months-old child presenting with non-ketotic hyperglycinemia (NKH). Seizures were generalized in both cases, with many myoclonic spasm and falls a day. Patients presented with major cognitive impairments, without focal neurological deficits, and mild cortical atrophy at MRI. VNS surgery was performed in standard way under microscope magnification. VNS stimulation was started 15 days after surgery, achieving maximal energy after 2 months. Mean stim values were 1.0 to 1.5 mA with a standard cycle; impedances were lower than 1200 Ohms.

Results: Patient 1, affected by Glutaric aciduria type II (GA II). Epilepsy occurred at the age of five months presenting with drug resistant epileptic spasms. The neurological status before the onset of epilepsy was normal. After the onset of epilepsy, a progressive neurological and cognitive impairment occurred. The seizures became drug-resistant. A first Status Epilepticus occurred at the age of six years. Epilepsy worsened over the years becoming drug resistant despite several mono and polytherapy. Seizures were of different kinds: generalized tonic, noise-provoked and spasms both during awake and sleep. At the age of 23 years he underwent VNS implantation. At one-year-follow up the seizures frequency decreased 50%, at most tonic seizures and spasm, and the severity of the post-ictal period improved.

Patient 2, affected by Non-ketotic Hyperglycinemia (NKH). Seizures occurred early after birth, initially treated with Phenobarbital. At the age of three months a first Status Epilepticus occurred, requiring admission to PICU. The child never was seizures free and the neurological status remained seriously impaired. At the age of 16 months a novel Status Epilepticus occurred and at that time, after parental consensus, VNS implant was performed. Unexpectedly the seizures frequency decreased to few brief seizures-a-day remaining unchanged for six months. At the last follow-up the seizures frequency was of 2 brief seizures-a-day without recurrence of Status Epilepticus.

Conclusion: Although the effective mechanism of VNS is still unclear, it may be assumed that depression of the cortical excitability should take place. Epilepsy in metabolic encephalopathy is due to increased cortical excitability, consequent to disruption of metabolic chains or to amassing of metabolites. After these considerations and considering our preliminary results, VNS should be suggested as a possible therapeutic tool in case of intractable epilepsy for metabolic encephalopathy.

#116

Diagnosis and surgical outcome of frontal lobe epilepsy: a case series report.

Xianlun Zhu (1), Danny Chan (1), Eva Fung (2), Howan Leung (3), Wai Poon (1), Hoitung Wong (1)

1. Division of Neurosurgery, Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China

2. Department of Paediatrics, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China

3. Division of Neurology, Department of Medicine and Therapeutics, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China

Introduction: Frontal lobe is the second common type of epilepsy surgery after temporal lobe epilepsy surgery. Seizure free rate after frontal lobe surgery is around 50% as compared to 70-80% after temporal lobe surgery. We aim to improve the outcome through reviewing the frontal lobe epilepsy surgery done in our institute.

Methods: All cases of frontal lobe epilepsy received resective surgery from 2000 to 2014 in our institute were reviewed. Engel's classification was used for the outcome evaluation.

Results: 100 epilepsy operations were performed. Among them, 56% were temporal lobe, 15% (15 cases 16 operations) were frontal lobe, and 29% were others. Of the 15 frontal lobe cases, 9 were male and 6 were female. The mean age was 21 years old (range: 45 days to 53 years old). The Mean follow-up period was 3 years (range: 6month to 12 years). The pathology were cavernous malformation 5 cases, low grade tumour 4 cases, focal cortical dysplasia (FCD) 4 cases, glioneuronal malformation 1 case and post-AVM excision scar 1 case. Subdural electrode for VEEG and extra-operative mapping were used in 2 cases. Awake craniotomy was used in 4 cases. Resting state fMRI plus intra-operative mapping were used for a case of 5 years old child. The seizure outcome was Engel's classification I in 11 cases (73%), II in 2 cases and III in 2 case. Among the 4 FCD cases, the MRI finding was genuine non-lesional in one case. In other three cases, the first MRI reported non-lesional but all turned out to be lesional in subsequent MRI. For the EEG findings, it was quite common that the seizure onset was massed by muscle artefact although ictal events were captured, while inter-ictal EEG provided useful information in lateralization and localization. In two cases with Engel's classification II and III respectively had incomplete excision of the lesion.

Conclusion: Frontal lobe epilepsy surgery is challenging. Good seizure outcome is about 40% in non-lesional cases and 70% in lesional cases. Our results are consistent with the literature. Issues in frontal lobe epilepsy surgery include [1] Diverse clinical manifestation; epileptic discharge from ictal scalp EEG can be bilateral, frontotemporal, or massed by muscle artefacts; [2] Difficulty in recognizing the subtle imaging abnormality in case of focal cortical dysplasia. Dedicated epilepsy MRI protocol, high resolution MRI, experiences are all important factors; [2] Incomplete excision is an unfavourable factor to seizure outcome, which can be due the eloquent area location of the epileptic focus. Various techniques can be used to enable complete excision. Our results also suggested that once a lesion was identified, surgical decision can be made together with one concordant investigation results satisfying lateralization and localization.

As discussed above, careful analysis of the information from investigations, improvement of MRI diagnosis together with the application of various surgical techniques contribute to the seizure free rate in frontal lobe epilepsy surgery.

#244

**Studies around the seizure related injuries in young patients and in young athletes.
Appropriate management in young individuals with epilepsy, with headache and
epileptic neurologic signs.**

Nikolaos Syrmos (1,2) , Andreas.Diamantopoulos (1) , Christos. Bechliyanides (1) , Georgios.Ampatzidis (2)

1. Medical School, Aristotle University of Thessaloniki, Thessaloniki, Macedonia Greece.

2. Department of Sports Science , Aristotle University of Thessaloniki, Thessaloniki, Macedonia Greece.

Aim of this study is to investigate the seizure related injuries and the appropriate management in young athletes with epilepsy .Also to investigate the headache together with epileptic neurologic signs in young patients and in young athletes. We studied -60 individuals-

- 20 cases- group a- of young athletes with epilepsy, the daily sports activity of these individuals and also the seizure related injuries

- 10 cases-group b- of young patients with epilepsy, the daily sports activity of these individuals and also the increase of the quality of life

- 20 cases- group c- of young athletes with epileptic neurologic signs and headache

- 10 cases –group d- of young patients with epileptic neurologic signs and headache

We conclude that further studies are warranted but seems injuries are common in patients with epilepsy , the can have severe consequences even fatal results Headache is often present in epilepsy and very often is a deteriorate fact of quality of life. We have to help and to support these young patients to participate in sports activity , always under medical surveillance.

#158

Epilepsia Partialis Continua responsive to subdural cortical stimulation

Ismail Ughratdar (1), Antonio Valentin (2), Jebet Cheserem (1), Robert Morris (3), Robert Elwes (4), Franz Brunnhuber (2), Nandini Mullati (2), Gonzalo Alarcon (2), Richard Selway (1)

1. Neurosurgery, King's College Hospital, London, UnitedKingdom

2. Neurophysiology, King's College Hospital, London, UnitedKingdom

3. Neurosurgery, Addenbrookes Hospital, Cambridge, UnitedKingdom

4. Neurology, King's College Hospital, London, UnitedKingdom

Introduction: Epilepsia partialis continua (EPC), is a rare form of status epilepticus which may affect an individual limb, and can be extremely disabling and refractory to medical therapy. In cases involving the motor cortex, surgical resection would result in significant deficit.

Methods: We present two patients with focal, drug-resistant EPC with significant functional deficits who underwent successful trial cortical stimulation followed by permanent implantation. Both patients also had frequent convulsive seizures.

Results: The first patient presented with subtle right hemiparesis and clumsiness of the hand, with otherwise normal tone and cortical sensations. After implantation, myoclonic jerks in the arm were clearly reduced and functional improvements were seen in drawings and handwriting in the following 10 months. When the stimulator battery ran out, EPC returned. After battery replacement, EPC resolved, and the patient is presently having a >80% reduction of seizures 16 months after cortical implantation

The second patient with EPC in his left leg presented with difficulty walking associated with hypertonia, spastic gait and abnormal posturing. Sixteen months after cortical implantation, his gait was markedly improved and the patient is able to walk without assistance. A >80 % improvement in frequency of seizures was also noted.

Conclusion: In both cases, the improvement in seizures and limb function has been sustained with concurrent improvements in their EEGs. This small case series echoes the findings in other small series of the efficacy of chronic neocortical stimulation in the management of these challenging and debilitating conditions.

#224

Immediate postimplantation effect of baseline stimulation parameters of vagus nerve stimulation in patients with refractory epilepsy

Maria Tormasiova (1), Aurelia Kollova (2), Ladislav Bratsky (3)
 1. Dept. of Neurology, University Hospital Kosice, Kosice, Slovakia
 2. Dept. of Neurosurgery, University Hospital Kosice, Kosice, Slovakia
 3. Dept. of Pediatric Neurology, Childrens Hospital, Kosice, Slovakia

Introduction: Vagus nerve stimulation is a palliative treatment in patients with refractory epilepsy, who do not fulfill the criteria for resective surgery. Effect of VNS therapy increases with the time since its implantation; to assess clinical benefit it is recommended to analyze time interval of two years. Around that time, there is about 50% of responders to the stimulation. We present a case reports of two patients, with longer seizure-free interval immediately after VNS implantation, with subsequent increase of seizures frequency without the change of stimulation parameters.

Methods: Between 2007-2013 we implanted VNS in 30 patients with refractory epilepsy. At the time of the analysis, all the patients had VNS for at least 1 year. Baseline stimulation parameters were as follows: output current 0.25 mA, frequency 20 Hz, pulse width 250 usec, ON time 30 sec., OFF time 3 mins. Impulse generator was turned on at the time of surgery.

Results: In two patients, there was a substantial reduction of seizures immediately after surgery, compared with the preoperative period. In 7- years old boy with Lennox-Gastaut syndrome, who had before the surgery seizures daily, they have disappeared for about four months after surgery. Subsequently, we have recorded increase in seizure frequency and 3 years after surgery the frequency of his seizures is the same compared to the period before implantation, despite different regimes of stimulation, including rapid cycling. The second patient, 20-years old man with mental retardation, autism a generalized seizures, with repeated myoclonic seizures and frequent atonic seizures was seizure free for 34 days after surgery. One year after surgery he is a responder with about 65% reduction of myoclonic seizures and total improvement of atonic seizures. Predictive value of postimplantation improvement we have not confirmed in our two patients.

Conclusion: We have recorded longer postimplantation seizure-free interval after VNS surgery on baseline stimulation parameters in two patients. There are few reports about similar cases in the literature. It is speculated, that the cause might be placebo effect, effect of Regarding prognosis of VNS effect during first months after surgery one has to be cautious, as good postoperative effect of VNS might not be the guarantee for good future effect. Knowing this aspect enables to prevent comments on „wrong programming“. This presentation is to initiate the discussion to share experience from different departments, because there is a lack of published data on this phenomenon.

2.4 Pain

#45

Diffusion tensor magnetic resonance imaging (DTI) tractography guided deep brain stimulation in neuropathic pain

Volker Arnd Coenen (1), Kristin Kieselbach (2), Irina Mader (3), Hans-Joerg Mast (3), Peter Reinacher (1)

1. Department of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Freiburg, Germany

2. Interdisciplinary Pain Centre, Freiburg University Medical Center, Freiburg, Germany

3. Department of Neuroradiology, Freiburg University Medical Center, Freiburg, Germany

Submitter: Mr Coenen Volker Arnd (DE)

Introduction: We report a patient who presented with a neuropathic trigeminal pain syndrome. Multiple therapeutic approaches including chronic motor cortex stimulation, intrathecal drug application and deep brain stimulation (DBS) to the periventricular/periacqueductal grey and sensory thalamus did not lead to a sustained relief of pain with a persistent rating of 7-9 on the visual analogue scale, indicating severe pain.

Methods: A magnetic resonance imaging scan was suspicious for a malposition of the previously implanted clinically non-functional DBS electrodes. The DBS system was completely removed and the patient underwent diffusion tensor magnetic resonance imaging (DTI). At the following day two DBS electrodes were implanted.

Results: DTI tractography analysis revealed that the initially placed DBS electrodes were touching the median polysynaptic pain system (MPNS) and that the supposedly thalamic electrode was marginally touching the same. The newly placed thalamic electrode now clearly involved the medial and trigeminal lemniscal system. His VAS dropped almost instantaneously and remained stable with fluctuating levels between 2 and 5. At a later stage PAG DBS was initiated. The patient felt additional relief from his disease burden.

Conclusion: This report strengthens the idea of the application of the DTI tractographic technology for DBS surgery in neuropathic pain. DTI tractography might provide a salvage strategy for situations in which previous DBS has failed and revision might be considered. According to our analysis the MPNS is confluent with the anterior thalamic radiation that is involved in processing of emotional pain.

#68

Spinal cord stimulation with surgical leads in local anesthesia and sedation.

Roberto Donati (1)

1. Neurosurgery, Azienda Papa Giovanni XXIII, bergamo, Italy

Submitter: Mr Donati Roberto (IT)

Introduction: The paddle (surgical) leads allow a better control of pain in the legs, in particular in FBSS but for their introduction is required surgery micro laminectomy. The improvement of anesthetic currently procedures allows to perform this surgical procedure under local anesthesia and sedation to allow a good cooperation of the patient. The author evaluates the effectiveness of pain control in spinal cord stimulation with paddle leads and he considers the tolerance and cooperation of the patients undergoing surgery micro laminectomy under local anesthesia and sedation

Methods: Since Maj 2010 the author performed the mini (micro) laminectomy in local anesthesia (in SCS) in 16 patients ; all patients were suffering from FBSS.
In 13 patients were used the paddle leads; in 3 patients were used percutaneous leads.

Results: All patients that have undergone surgical treatment have obtained good pain control; pain relief that obtained during surgery was stable in the postoperative period.
In 3 patients were introduced percutaneous leads (during micro-laminectomy) because of anatomical conditions (2 pzs) and tolerance (1 pzs).

Conclusion: Local anesthesia with sedation (drugs) has proved to be a good technique to allow good collaboration of the patients during micro-laminectomy to place a surgical (paddle) leads

#86

Expanded DREZ (Dorsal Root Entry Zone) -lesion for intractable pain following brachial plexus avulsion injury

Taniguchi Makoto

Submitter: Mr TANIGUCHI Makoto (JP)

Introduction: Although lacking in hard evidence, DREZ-lesion is known to be one of the most powerful and effective method of choice to alleviate intractable pain following Brachial Plexus Avulsion injury (BPA).

Methods/results: Since this maneuver was introduced in the early '70s when the mechanism of central neuropathic pain and its treatment were not well understood, its appropriate position in the treatment ladder for intractable pain following BAP remains still uncertain. Also remains uncertain are its real efficacy and long-term results.

Conclusion: To our knowledge, there are at least two different methods for distracting dorsal horn, being whether by manually or by electrocoagulation.

#174

VPM-DBS 10 years after VPM thalamotomy to treat a recurrent facial pain

Yves Yamgoue (1), Etienne Pralong (2), Marc Levivier (2), Jecelyne Bloch (2)

1. Neurosurgery, CHUV, Lausanne, Switzerland

2. Neurosurgery, CHUV, Lausanne, Lausanne, Switzerland

Submitter: Mr Yamgoue Yves (CH)

Introduction: We report here the successful treatment of recurrent facial pain by ventro-postero median thalamic nuclei deep brain stimulation (VPM-DBS) many years post VPM thalamotomy

Methods: A 62 year old woman who suffered from an atypical V1 V2 right side nevralgia was successfully treated a decade ago with a surgical VPM thermocoagulation. 10 years later, the pain progressively recurred and resisted to medical treatments.

A DBS procedure was proposed to the patient aiming to stimulate the vicinity of the preexisting lesion. The stereotactic targeting was based on a stereotactic CT scan acquired the day of the surgery, fused on the Medtronic Stealth Station with an MPRage gadolinium 3Tesla MRI obtained previously. The target was centered on the antero-lateral side of the visible thalamotomy with possibilities to explore four surrounding trajectories.

The surgery was performed under local anesthesia. A micro electrode was inserted through the first planned trajectory. Micro stimulations were performed from 6 mm above the target to the target at a frequency of 200HZ and a pulse with of 90 μ s. Electrode location was confirmed with the O-arm.

Results: Intra operatively, during the first stimulation trials, the pain relief was immediate at low intensities, paresthesia in the face and arm were felt by the patient at higher intensities. After the first trajectory the pain did not recur, therefore no further exploration was performed and a 3387 Medtronic electrode was inserted to the target.

After a week of external stimulation providing constant pain relief, the electrode was internalized and connected to an Activa SC 602 Medtronic.

Conclusion: Neuropathic pain is a dynamic process that can involve time. This observation suggests that VPM-DBS is still possible close to previous lesions and can successfully achieve facial pain relief 10 years after VPM thalamotomy.

#207

Hypothalamic deep brain stimulation in the treatment of chronic refractory cluster headache: An extended long-term follow-up

Goetz Luetjens (1), Assel Saryyeva (1), Hans-Holger Capelle (2), Christoph Schrader (3), Joachim K. Krauss (2)

1. Neurosurgery, Medical School Hannover, Hanover, Germany

2. Neurosurgery, Medical School Hannover, Hannover, Germany

3. Neurology, Medical School Hannover, Hannover, Germany

Submitter: Mr Lütjens Götz (DE)

Introduction: Cluster headache (CH) is a primary headache disorder and is characterized by sudden massive pain in the orbital, supraorbital and temporal region that lasts between 15 and 180 minutes if not treated and usually is accompanied by tearing, nasal congestion and lacrimation. Since chronic CH was found to be refractory to medical therapy in some patients, deep brain stimulation (DBS) in the posterior inferior hypothalamus was introduced in the 2001 by Leone et. al in Milano. We here report on the extended long-term outcome of three patients with chronic CH treated with hypothalamic DBS.

Methods: In three men with severe chronic cluster headache underwent DBS in the ipsilateral posterior inferior hypothalamus. Electrodes were implanted stereotactically computer tomography (CT) based (model 3389, Medtronic, MN, USA). Pain assessment was performed prä- and postoperatively using VAS, global rating scale of therapy, frequency attacks and quality of life was investigated using the SF-36. Follow-up time was 48-84 months.

Results: In two patients, both intensity and frequency of the attacks were reduced (frequency 70% and 80%, intensity 90% and 60%) after surgery, whereas in one patient there was no significant change. Long-term evaluation at 72 and 86 months postoperatively in the first two patients showed sustained significant pain reduction (80% of frequency, 70 % of pain intensity). The stimulation parameters for deep brain stimulation were: 1,4-4,4 V, 130 Hz, 60µs, bipolar stimulation. However, in one patient CH reoccurred on the other side 86 months after the initial treatment.

Conclusion: DBS in the posterior hypothalamus can be an effective therapeutic option for selected patients with chronic CH. If DBS is effective, benefit can be stable on the long run. Occipital nerve stimulation nowadays, however, has become an alternative therapy in chronic CH. There is no data available which method would be preferable for long-term treatment.

#216

The clinical efficiency of spinal cord stimulation for refractory angina pectoris

Vladimir Murtazin (1), Andrey Ashurkov (2), Vladimir Shabalov (2), Abdyrakhman Duishobaev (3), Alexey Krivoschapkin (2)

1. Neurosurgery, Novosibirsk State Medical University, Novosibirsk, Russia

2. Neurosurgery, Novosibirsk Research Institute of Circulation Pathology named after academician E. N. Meshalkin, Novosibirsk, Russia

3. Neurosurgery, Railway Clinical Hospital, Novosibirsk, Russia

Submitter: Mr Murtazin Vladimir (RU)

Introduction: Angina pectoris (AP) is a chronic condition characterized by presence of angina, caused by coronary insufficiency in presence of coronary artery disease, which cannot be adequately controlled neither by combination of medical therapy nor by vascular surgery treatment (angioplasty and coronary artery surgery). According to 2002 American Heart Association guidelines, spinal cord stimulation (SCS) is a class IIb alternative therapy for treatment of AP. In general, SCS is a neuromodulation therapy that appears to be an effective and safe option for these patients.

Methods: We applied SCS in 5 patients with refractory angina pectoris. The first step procedure was trial neurostimulation to reveal the efficacy of pain relief before the second step to implant the permanent neurostimulation system. Prone position and local anesthesia were used. A 14-gauge Tuohy needle was inserted in the Th7-Th8 interlaminar space under fluoroscopic guidance. The epidural space was identified using a loss-of-resistance technique. Percutaneous lead 3086 (St. Jude Medical Inc., Minnesota, USA) was inserted in the epidural space at the C7-Th1 level. Implantable pulse generator (IPG) Eon C (St. Jude Medical Inc., Minnesota, USA) was implanted into subcutaneous space of left upper external quadrant of the buttock. Myocardium perfusion scintigraphy (MPS) was performed on admission and the 7th-10th days after the procedure to estimate the efficacy of treatment. In addition, visual analogue scale (VAS) was used to assess the degree of pain both in rest and physical activity. Patients were evaluated at 6 and 12 months. There were estimated changes of electrocardiography, the position of epidural leads, subjective assessment of pain, improvement in exercise tolerance, and dependence of nitrates.

Results: The patients showed $8,14 \pm 0,2$ points according VAS before the procedure and pain reduced to $1,29 \pm 0,22$ ($p < 0,01$) after the surgery. All of the patients demonstrated the rise of tolerance to physical activities and reduction of antianginal drugs consumption. MPS detected the increase in coronary reserve from 9 to 3 prearranged units. There were no procedural complications observed. During the observation period in a year has seen an improvement in quality of life (SF-36) by an average of 27% compared to baseline.

Conclusion: Patients with refractory angina pectoris suffer from severe symptoms and impaired activities of daily living. Our experience demonstrates that SCS is a minimally invasive technique to reduce pain and improve quality of life with coronary reserve enhancement in this patient cohort.

#217

The clinical efficiency of spinal cord stimulation for peripheral vascular disease

Vladimir Shabalov (1), Vladimir Murtazin (2), Andrey Ashurkov (1), Abdyrakhman Duishobaev (3), Alexey Krivoschapkin (1)

1. *Neurosurgery, Novosibirsk Research Institute of Circulation Pathology named after academician E. N. Meshalkin, Novosibirsk, Russia*

2. *Neurosurgery, Novosibirsk State Medical University, Novosibirsk, Russia*

3. *Neurosurgery, Railway Clinical Hospital, Novosibirsk, Russia*

Submitter: Mr Murtazin Vladimir (RU)

Introduction: Peripheral vascular disease (PVD) is chronic severe pain condition, caused by peripheral artery diseases, which cannot be adequately controlled neither by combination of medical therapy nor by vascular surgery treatment (angioplasty and peripheral artery surgery). PVD prevalence in the United States has ranged as high as 30% in adult populations and is closely associated with elevated risk of cardiovascular disease morbidity and mortality. Spinal cord stimulation (SCS) is a neuromodulation therapy that appears to be an effective and safe option for these patients.

Methods: We applied SCS in 17 patients with critical limb ischemia. The first step procedure was trial neurostimulation to reveal the efficacy of pain relief before the second step to implant the permanent neurostimulation system. Prone position and local anesthesia were used. A 14-gauge Tuohy needle was inserted in the L3-L4 interlaminar space under fluoroscopic guidance. The epidural space was identified using a loss-of-resistance technique. Percutaneous lead 3086 (St. Jude Medical Inc., Minnesota, USA) was inserted in the epidural space at the Th12-L1 level. Implantable pulse generator (IPG) Eon C (St. Jude Medical Inc., Minnesota, USA) was implanted into subcutaneous space of left upper external quadrant of the buttock. Doppler flowmetry (LDF) and transcutaneous oximetry (TCO) were performed on admission and the 7th-10th days after the procedure to estimate the efficacy of treatment. In addition, visual analogue scale (VAS) was used to assess the degree of pain both in rest and physical activity. Patients were evaluated at 6 and 12 months. There were estimated changes of tissue oxygenation, the position of epidural leads, subjective assessment of pain, improvement in exercise tolerance, and dependence of analgesics.

Results: The patients showed $9,27 \pm 0,15$ points according VAS before the procedure and pain reduced to $2,07 \pm 0,03$ ($p < 0,01$) after the surgery. All of the patients demonstrated the rise of tolerance to physical activities and reduction of drugs consumption. TCO showed microcirculation improvement in the form of oxygen saturation's increase from 7 to 70 mm Hg on the shin and from 20 to 68 mm Hg on the back of foot. There were no procedural complications observed. During the observation period in a year has seen an improvement in quality of life (SF-36) by an average of 58% compared to baseline.

Conclusion: Patients with critical limb ischemia suffer from severe symptoms and impaired activities of daily living. Our experience demonstrates that SCS is a minimally invasive technique to reduce pain and improve quality of life with vascular reserve enhancement in this patient cohort.

#236

Radiofrequency at Foramen Ovale approach for Trigeminal Neuralgia. How selective can it be?

Jean Ciurea (1)

1. *Functional Neurosurgery, Cl Emerg. Hospital " Bagdasar-Arseni", Bucuresti, Romania***Submitter:** Mr Ciurea Jean (RO)

Introduction: A total number of 325 patients with trigeminal neuralgia in maxillary and mandibular branch were operated during the last 5 years. Selective RFT at foramen ovale was used. That was obtained by careful stimulation of fiber with topographic specificity.

Methods: The best results are obtained when the patient is awake and cooperative. The local anesthesia is not enough for patient pain protection, and in certain cases an i.v. drug such as propofol must be used. The recovery from this is sometimes prolonged and the threshold for pain is risen up making the functional localization more difficult. I used this approach as it follows:

Patient is informed on the procedure and insisted on painful part of it, which can be controlled by local anesthesia and propofol, if necessary. The needle for local anesthesia is first introduced on trajectory of the electrode, 5 to 10 ml of xilin 1% injected, then removed and re introduced through sigmoid incisures of mandible immediately under zygomatic arch. If proper direction is maintained, just behind the external pterigoid plate, the trigeminal nerve is targeted under its exit at foramen ovale. Injection of 5 ml of xilin 1% will allow after 1 minute the piercing of foramen ovale diaphragm with less pain, enabling motor and sensitive testing of the nerve. Stimulation of nerve at high frequency (120Hz) will make lesioning more tolerable for the patient.

Results: There were no major complication despite the anatomical challenges for this procedures. No suicidal attempt was recorded after surgery. Most of Gasser radiofrequency patients are discharged after 12 to 24 hrs. Post surgery, the amount of medication is lowered, but do not cut to null. Relapse is encountered after a mean of 6 -48 months. It represent 12% at 5 years in our series. RFT can be effective in case of second or even third recurrences.

Conclusion: Radiofrequency is supraselective vs. gammaknife, compression and glycerol. Gamma knife presents a median to response 4 wks (1 D – 4 M). It Improves 86% vs. more than 90% in all others methods. All above mentioned procedures are safer for older patients when compared to neurosurgery. Not neglectable at all, radiofrequency is less expensive then other methods. It is obvious that large prospective randomized multi centric studies are necessary for the next future practice standards.

#251

Intrathecal Baclofen effect on central or peripheric neuropathic pain: a retrospective, multicenter, single-blind study on 23 patients

Vincent d'Hardemare (1), Jean Bruxelles (2), Anne Margot-Duclos (3), Maximilien Bachelart (4), Jean-Baptiste thiebaut (5)

1. Neurosurgery, Fondation Ophtalmologique A. de Rothschild, Paris, France

2. Pain Treatment Department, Fondation ophtalmologique A. de Rothschild, paris, France

3. Pain treatment Department, fondation ophtalmologique A. de Rothschild, Paris, France

4. Neurosurgery, Fondation Ophtalmologique A. de Rothschild, Paris, France

5. Neurosurgery, Fondation ophtalmologique A. de Rothschild, paris, France

Submitter: Mr d'Hardemare Vincent (FR)

Introduction: despite many drugs or surgical therapies, some central or peripheral neuropathic pains are refractory. The authors report the results on pain of a series of patients who had intrathecal injections of Baclofen and placebo.

Methods: between January 2009 and December 2013, 28 patients were hospitalised in the Department of Neurosurgery to receive injections of Baclofen to treat refractory neuropathic pain. As a first step, an intrathecal catheter and a subcutaneous site were implanted. Then, Baclofen was injected once a day, from 50 Gamma to 100 Gamma. The increase of the dose was stopped when a benefit was noticed. Finally, Baclofen and salt solution were alternatively injected. The patients didn't know when this modification would take place. During the eight hours following the injection, the pain was rated each hour on a visual analogue scale (VAS).

Results: Among these 28 patients, 23 were included in our retrospective study. The initial VAS was 6.6/10. In average, pain decreased of 15% when placebo was injected, whereas the decrease was of 58% with Baclofen. 15 patients on 23 noticed a real positive effect with Baclofen during several hours. The injections of Baclofen are efficient more rapidly when the pain is in the inferior limbs, and the best responders were the patients with a pain secondary to a lesion of the cauda equina. Many of these patients had a sub-cutaneous implanted pump and the effect of tests subsequently confirmed.

Conclusion: The analgesic effect of Baclofen for neuropathic pain is hereby established. To confirm the results of our retrospective study, a randomized double-blind multicenter prospective study was launched in September this year and will last 2 years

#252

Dorsal Root Entry Zone lesioning for pain after a lombo-sacral plexus avulsion: a study in a 9-patients consecutive series.

Vincent d'Hardemare (1), Anne Margot-Duclos (2), Jean Bruxelles (3), Maximilien Bachelart (4), Jean-Baptiste thiebaut (5)

1. Neurosurgery, Fondation Ophtalmologique A.de Rothschild, Paris, France

2. Pain treatment Department, fondation ophtalmologique A. de Rothschild, Paris, France

3. Pain Treatment Department, Fondation ophtalmologique A. de Rothschild, paris, France

4. Neurosurgery, Fondation Ophtalmologique A. de Rothschild, Paris, France

5. Neurosurgery, Fondation ophtalmologique A. de Rothschild, paris, France

Submitter: Mr d'Hardemare Vincent (FR)

Introduction: brachial plexus avulsion are well described and the consecutive paroxysmal pain can be treated by a selective lesioning of the dorsal root of the cervical medulla. However, avulsions of the root of conus medullaris remain unknown. The authors described their results about the treatment of pain after avulsion of the cauda equina.

Methods: Over the last 10 years, 9 patients have been treated in our department for refractory pain in the inferior limb secondary to root avulsion of the cauda equina. Among them, 8 benefited from destruction of the dorsal root entry zone (DREZ), 1 patient was relieved thanks to an intra-theal therapy of Baclofen without a DREZ. The evaluation before and after surgery was done with pain questionnaire (Visual Analogic Scale, Neuropathic Pain Diagnostic Questionnaire DN4).

Results: the pain profile was similar for all the patients . This neuropathic pain occurred a long time after the accident where predominate paroxysms with electric shocks in the dermatoma concerned. MRI revealed pseudo-meningocela similar to those after avulsion of brachial plexus avulsion. No complication was reported after the DREZotomy and a significant improvement was obtained. 1 patient showed paresthesia. Drugs were reduced essentially for morphinic but also for others drugs. For the patient with baclofen intra-theal, after a 8 years follow-up, a total improvement is obtained since the beginning.

Conclusion: With appropriate patient selection, DREZ lesion is an efficacious and durable procedure that can be performed with low morbidity and good patient outcomes. The benefits for a DREZ depend of the quality of the lesion. Nevertheless, intrathecal Baclofen seems to be an alternative but it is only a case report.

2.5 Spasticity

#21

Optimization of the Treatment of Spasticity in Patients after severe Spine Trauma.

Artur Biktimirov (1), Albert Sufianov (2), Vladimir Shabalov (3), Alexander Orlov (1), Tatiana Tubaeva (1), Sergey Churkin (1), Evgeniy Matveev (1)

1. *Functional neurosurgery, "Federal Centre of Neurosurgery", Tyumen, Russia, Tyumen, Russia*

2. *Neurosurgery, "Federal Centre of Neurosurgery", Tyumen, Russia, Tyumen, Russia*

3. *Functional Neurosurgery, "Federal Centre of Neurosurgery", Tyumen, Russia, Tyumen, Russia*

Submitter: Mr Biktimirov Artur (RU)

Introduction: Treatment of the consequences of traumatic damage of the spine and spinal cord is one of the most acute issues in the modern world. Development of heavy spasticity syndrome after spinal cord injury is widely spread and comprises up to 60% of all cases according to different sources of literature. The aim of the research is to optimize medical assistance to the spinal cord injury patients with spasticity syndrome.

Methods: Our research is based on the analysis of 23 cases. All patients suffered from heavy spasticity syndrome after spinal cord injury which made impossible the process of rehabilitation and lowered the quality of life. The average level of spasticity was $3,1 \pm 0,4$ points Ashworth scale. The patients presented in the study underwent surgery from April 2012 to March 2014. Among them are 16 patients who were implanted systems for spinal cord stimulation (SCS): systems "EonC" and "EonC mini" produced by St. Jude Medical, and systems "Prime Advanced" by Medtronic. Seven patients were implanted programmable pumps for chronic intrathecal baclofen therapy (ITB) "Medstream II" by Codman. The patients were selected for the treatment the following ways. At the first stage the patient was implanted an electrode for stimulation in the area of lumbar enlargement of spinal cord, then trial spinal cord stimulation procedures were carried out for the next three to five days. If the stimulation caused the decrease of spasticity to the comfortable level for the patient, we implanted the system for chronic stimulation of the spinal cord. If the patient did not respond to the stimulation or we could not obtain the decrease of spasticity up to the comfortable level, then the baclofen trial was carried out. If the baclofen trial brought to the decrease of the muscle tone up to 1 point Ashworth scale, then the baclofen pump was implanted.

Results: As a result of the treatment in 100% of cases patients experienced the decrease of spasticity level. The muscle tone decrease in the patients with implanted baclofen pumps comprised in average $2 \pm 0,3$ points Ashworth scale. The patients with implanted stimulators experienced the decrease of spasticity as well, but in contrast to the cases with implanted baclofen pump, they could regulate the level of spasticity depending on their physical activity. That means that if necessary patients had the possibility to increase the muscle tone up to the initial level or decrease it up to 1 point Ashworth scale.

Complications. One patient with implanted pump twice had the pump catheter damaged as the result of intense physical activity. Another patient had problems with incorrect functioning of the pump which was solved by replacing the pump.

The patients with implanted stimulators experienced the following complications. One patient had the electrode damaged, and the electrode was replaced. In the second case the impulse generator broke down and was replaced, too.

Conclusion: Despite the fact that baclofen pump is the mostly used around the world, the results of our research has shown that the method of spinal cord stimulation is not less effective in the treatment of heavy spasticity syndrome after spinal cord injury and might be applied in the world practice along with baclofen therapy.

#142

Neurostimulation for myelopathy. Fecal incontinence treatment using spinal cord stimulation.

Oleg Kamadey (1), Gennadiy Alekseev (1), Irina Poverennova (2), Evgeniy Krivoshchekov (3)

1. Neurosurgery department, Samara Regional Hospital, Samara, Russia

2. Neurology and neurosurgery department, Samara State Medical University, Samara, Russia

3. Surgery department, Samara State Medical University, Samara, Russia

Submitter: Mr Kamadey Oleg (RU)

Introduction: Myelopathy of various genesis is often accompanied by pharmacoresistant spasticity, neuropathic pain syndrome and pelvic dysfunction. The most often causes of myelopathy are spinal injury (53,07 %), FBSS (19,4 %), spinal stroke (12,03%), multiple sclerosis (9,26%), spondylodiscitis (5,56%).

Methods: Samara Regional Hospital neurosurgery department use chronic epidural neurostimulation systems (SCS) implanting in the posterior epidural space to patients with myelopathy of various genesis as a part of a complex therapy .

37 patients were operated (25 men and 12 women, age 22 - 75 years): in 12 cases it was a damage of spinal cord on cervical region, in 20 cases - thoracic region and in 5 cases – lumbar region of the vertebral column.

Results: The result of neurostimulation is pain relief from 53 to 18 points using the Visual analog scale, muscle tone decreasing from 2,8 to 1,35 points of Ashworth Scale.

Clinical example. Patient, a male born in 1960, with L4 disc herniation, that was removed in 2008. After operation the patient walked with crutches because of weakness of feet extensors and hallux on both sides (1,5-2 points) and had fecal incontinence (Wexner score of 11). In 2010 in his back epidural space (D12-L1 level) was implanted the chronic neurostimulation system Medtronic Itrel3 with flat electrode Medtronic resume II. In six months the power in feet increased (3-3,5 points, now he walks without crutches) and fecal incontinence indicators improved to 5 points of Wexner scale. Catamnesis is 4 years.

Conclusion: If patient selection for operation is correct, the result of neurostimulation is reduction in pain, effective decreasing of spasticity, restoring the function of pelvic organs.

#144

INDICATION TO IMPLANT INTRATHECAL BACLOFEN (ITB) PUMP IN WALKING PATIENTS: EXPERIENCE ON EXTERNAL CONTINUOUS TEST

Alessandro Dario (1), Francesca Tonini (2), Michele Bertoni (3), Daniela Biacchi (4)

1. functional neurosurgery, Varese Regional Hospital, Varese, Italy

2. Department of Rehabilitation, Hospital Cuasso al Monte, Varese, Italy

3. Department of Rehabilitation, Department of Rehabilitation, Varese, Italy

4. Department of Rehabilitation, Hospital Cuasso al Monte, Varese, Italy

Submitter: Mr dario alessandro (IT)

Introduction: Baclofen is a gamma-aminobutyric acid (GABA) that inhibits excitation of central and peripheral motor neurons and suppresses spasticity by linking pre- and post-synaptic GABA β -receptors.

This study aims to spread specific indications to ITB definitive pump implant in walking patients affected by spasticity testing both functional effects through temporary ITB device and spasticity decrease.

Methods: The sample was constituted by six males patients affected by spasticity.

All patients were implanted with temporary programmable electronic pump ITB (SynchroMed Infusion System Medtronic).

Time from initial disease onset to implantation was about 4,5 years (range 1-17).

All patients were treated in Neurosurgical Day Hospital (Ospedale di Circolo – Fondazione Macchi in Varese). The average age at implantation was 43 years old (range 30-61)

) between 2011 and 2013, then they followed rehabilitation program in Department of Rehabilitation of the same hospital.

Initial baclofen dose at T0 was 48 mcg/die.

The dose of baclofen was increased every 24 hours by 24 mcg (T0 initial dose= 48 mcg/die, T1= 72 mcg/die, T2= 96 mcg/die, T4= 120 mcg/die, T5= 144 mcg/die).

Patients have been evaluated at the initial dose and after 24 hours the increase in the dosage of baclofen by functional tests in blind: Timed 10 meter walk test, six minutes walking test, (6MWT), Time up and go test, Ashworth Scale.

Subjective safety was assessed with self-reported visual analogic scale.

Results: We assessed an Ashworth Scale decrease in all patients at T1.

6MWT and 10 meter walk test demonstrated an increase at T2 and T3.

The execution of time up&go test decreased at T2 and T3 in all patients.

Subjective safety was increased at T3.

A dislocated catheter was reported in one case.

Conclusion: Through this study we can infer that indication of ITB definitive pump implant is based on functional improvement rather decrease of spasticity.

2.6 Neuroimaging

#17

Volumetric analysis of the subthalamic and red nuclei based on magnetic resonance imaging in patients with Parkinson's disease

İlkay Camlıdag (1), Ersoy Kocabicak (2), Bunyamin Sahin (3), Ali Jahanshahi (4), Lutfi Incesu (1), Dursun Aygun (5), Onur Yildiz (5), Yasin Temel (6)

1. Department of Radiology, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

2. Department of Neurosurgery, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

3. Department of Anatomy, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

4. Departments of a Neuroscience and b Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

5. Department of Neurology, Ondokuz Mayıs University, School of Medicine, Samsun, Turkey

6. Departments of Neuroscience and Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

Submitter: Mr Kocabicak Ersoy (TR)

Introduction: Parkinson's disease (PD) is associated with degeneration of the dopaminergic neurons in the substantia nigra. The subthalamic nucleus (STN) plays a pivotal role in the pathogenesis. However, there is not much known about the morphological changes in the STN. The red nucleus (RN) has many connections with the motor coordinating pathways although it is not primarily involved in the pathogenesis. In this study we aimed to compare the volumes of the STN and RN measured by magnetic resonance imaging in PD patients and controls to investigate how these structures are affected at the morphological level.

Methods: Twenty patients with PD and twenty age/sex matched controls were enrolled in this study. Severity score was determined by Hoehn & Yahr staging: 6 at stage II and 14 at stage III in med-off state. Imaging was performed by a 1.5 Tesla (T) MR scanner. Measurements of total brain and normalized STN and RN volumes were performed by manual planimetry using Image J software.

Results: No statistically significant differences were observed between two groups based on age or gender and disease stage and nuclei volumes. The total estimated brain volumes were not different between PD patients and controls. However, normalized volumes of the STN and RN were 14% and 16% larger, respectively, in PD patients compared to the controls ($p < 0.05$).

Conclusion: Our findings suggest that the volumes of the STN and RN are increased in patients with PD. These changes possibly reflect the altered metabolic activity of these regions demonstrated by neurophysiological studies.

#34

Anatomy of Subthalamic Nucleus with Correlation of Deep Brain Stimulation

BARAN YILMAZ (1), AKIN AKAKIN (1)

1. NEUROSURGERY DEPARTMENT, BAHCESEHIR UNIVERSITY, ISTANBUL, Turkey

Submitter: Mr AKAKIN AKIN (TR)

Introduction: Subthalamic nucleus (STN) is an important part of the brain related with Parkinson's disease and other involuntary movements. Subthalamic nucleus contains some fibers which travel to the cortical area and basal ganglia¹. Subthalamic nucleus is located just supero-medial to the red nucleus and substantia nigra. STN is widely acknowledged as an important modulator of basal ganglia output, and it receives its major afferents from the cerebral cortex, thalamus, globus pallidus externus and brainstem. Subthalamic nucleus projects mainly to both segments of the globus pallidus, substantia nigra, striatum and brainstem. The STN is essentially composed of glutamatergic neurons. Lesions of the STN induce choreiform abnormal movements and ballism on the contralateral side of the body^{1,2}. Despite the current interest, little is known about the relation between function of the STN and movement. In this study, we describe the anatomical relationship between the subthalamic nucleus and surrounding structures.

Methods: The cerebral hemispheres and cerebrums of 5 human cadavers are fixed in a 10%-formalin solution for at least 3 weeks. The first step in the preparation of the specimens is the removal of the arachnoidal and vascular structures by using surgical magnification (6x40). The hemispheres are frozen at -16°C for 2 to 4 weeks. Twenty-four hours after completion of the freezing process, the white fiber dissection is done with fine and self-shaped wooden spatulas. We take numerous digital photographs during dissections and fused the images by using a specific software (Anamaker 3D; available free from www.stereoeye.com), we fused the images to obtain an anaglyphic image.

Results/conclusions: The subthalamic nucleus is a small, lens-shaped nucleus in the brain. The STN is a part of the basal ganglia system and is located at ventral to the thalamus, dorsal to the substantia nigra and medial to the internal capsule. Anterior and lateral borders of the STN are enveloped by fibers of the internal capsule that separates this nucleus laterally from the globus pallidus. Postero-medially, the STN is very close to the red nucleus. The ventral borders of the STN are the cerebral peduncle and the substantia nigra. Dorsally, the STN has a border with the fasciculus lenticularis, which separates STN from the ventral thalamus.

Several fiber tracts courses near the borders of the STN. The subthalamic fasciculus consists of fibers that interconnect the STN and globus pallidus. This fiber bundle arises from the infero-lateral border of the STN.

The ansa lenticularis consists of fibers from the globus pallidus internus (GPi) that projects towards the thalamus. It originates mainly from the lateral portion of the GPi; coursing in a medial, ventral and rostral direction; sweeping anteriorly around the posterior limb of the internal capsule. This tract arises from the medial aspect of the GPi, perforates the internal capsule, and forms a bundle ventral to the zona incerta. Although some fibers from the lenticular fasciculus are dorsal to the STN, most of this tract courses rostral to the nucleus. Fiber tracts lying posterior to the STN include the medial lemniscus, spinothalamic tract, trigeminothalamic tract.

Especially, the dorsal aspect of the lateral portion of the rostral two-thirds and the caudal third of the nucleus are in relation with motor circuits. Subthalamic afferent fibers, cortico-subthalamic projections, and most of the cortical afferents to the STN are arising from the primary motor cortex, supplementary motor area (SMA), pre-SMA, and pre-motor area.

The fibers travelling between the red nucleus and subthalamic nucleus are called as habenular commissure at midline sections of the brain. The mamillary body is located at anterior to the subthalamic nucleus. The mamillothalamic pathway is located at antero-superior to the STN.

Atlas-Based Localisation of the Subthalamic Region: Using the 3 spatial MR imaging planes and applying the anatomical knowledge acquired by the cadaveric dissections, we can localize the subthalamic region. The subthalamic region is located at ventral to the thalamus, medial to the internal capsule, lateral and caudal to the hypothalamus. The nuclei found within the subthalamic region include the subthalamic nucleus and zona incerta. The STN has very close relationship with the substantia nigra and the red nucleus.

#55

Thalamic deep brain stimulation for complex tremor in multiple sclerosis: a case report and analysis of side effects related to fiber tracts

Höllig Anke (1), Sonny Tan (1), Björn Falkenburger (2), Yasin Temel (3)

1. Department of Neurosurgery, RWTH Aachen University, Aachen, Germany

2. Department of Neurology, RWTH Aachen University, Aachen, Germany

3. Department of Neurosurgery, University Hospital Maastricht, Maastricht, Netherlands

Submitter: Melle Höllig Anke (DE)

Introduction: Tremor is a severely disabling symptom in multiple sclerosis. The estimated incidence of this symptom lies between 25 and 60%. It is often a complex tremor and difficult to manage conservatively. In the context of the surgical treatment, deep brain stimulation (DBS) has been proposed in medically refractory tremor in multiple sclerosis, but there is no consensus about the optimal target. Retrospective analysis of cases including complications and pitfalls in addition to clinical trials may improve future treatment strategies. Here, we report a case of complex tremor in a multiple sclerosis patient treated by thalamic DBS and the imaging techniques we used to retrospectively analyze the effects of DBS.

Methods: A 43-year old right-handed female patient suffered from a severely disabling, predominantly right sided postural and intention tremor. Different types of medical treatment did not provide satisfactory tremor suppression. Unilateral DBS was performed targeting the left thalamic ventral intermediate nucleus (VIM) with the caudal contact implanted in the posterior subthalamic area (PSA).

Results: Intra-operative microelectrode recordings revealed the presence of typical thalamic cells. Recordings were particularly useful to identify the transition between the caudal border of the VIM and the PSA. DBS effectively alleviated both postural and intention tremor. One year after surgery the patient still clearly benefits from the intervention. However, suppression of postural tremor is now more pronounced than intention tremor. With stimulation of contact 0 as the negative contact and contact 3 as the positive contact the best tremor reduction is achieved at higher voltages (from 4V on). However, these stimulation parameters induce dysarthria. Fiber tracking based on diffusion tensor imaging (DTI; 1mm³ Voxels, 32 gradient directions) illustrated the close proximity of both the dentate-rubral tract (DRT) and the pyramidal tract (PT) to contact 3 of the stimulating electrode. Contact 0, 1 and 2 are located within DRT. Therefore, it may be speculated that dysarthria occurred due to interference of activated tissue with the corticobulbar tract under bipolar stimulation caused by a nearby located positive contact.

Conclusion: This case illustrates that DTI tractography is helpful to refine stimulation paradigms and understand mechanisms of side effects in DBS. This is of particular importance to improve DBS treatment strategies for rare indications and indications with heterogeneous lesions (such as MS or post-stroke dystonia).

#59

Identification of blood vessels with micro duplex ultrasound in Stereotactic Functional Neurosurgery

Wilhelm Eisner (1), Samuel Basler (2)

1. Neurosurgical, medical university innsbruck, austria, innsbruck, Austria

2. Basler AG Zürich, Basler AG Zürich, Zürich, Switzerland

Introduction: In 1982 transcranial duplex ultrasound sonography got introduced to the medical community by Rune Aaslid. Soon transcranial duplex sonography became the bedside method in monitoring of patients with subarachnoidal hemorrhages and vasospasm. Small ultrasound probes with diameters around 2.5 mm were used around 1990 in stereotactic and vascular neurosurgery. We and few others are utilizing intraoperative duplex ultrasound sonography in stereotactic procedures like diagnostic biopsies. The smallest range in diameter of the probes varies from 1.3 mm up to 2.5 mm. Considering certain rules stereotactic surgery is very safe. One of these rules is: never penetrate the brain by a sharp edged instrument like an intravenous needle – it will cause a bleeding. All tips of stereotactic instruments are rounded like dolphin noses. Microrecording electrodes are able to carry a higher risk of bleeding because of its sharp (2-3 μm) tungsten electrode tip. Multichannel microrecording is able to increase the risk of intracerebral bleeding because more brain penetrations per operation and because of the anatomy of the electrode.

Methods: We developed in 2000 the prototype of an intraoperative duplex ultrasound probe with a diameter less than 0.8 mm. The probe is fitting into the microelectrode guide tubes and is able to examine the trajectories of microrecording electrodes for blood vessels unseen in imaging bearing the risk of a hemorrhage.

Results: In the last 12 years a single subcortical bleeding occurred in our patients. It occurred while inserting five microelectrode guide tubes transcortically by touching the subarachnoidal space in a sulcal depth. It was not causing a neurological deficit but it was visible in the routinely performed postoperative stereotactic control CT. We will demonstrate the instrument and its usage. The development and utilization of that instrument is supported by our surgical data.

Conclusion: In 30 years duplex ultrasound examinations has proven its value for stereotactic surgery.

#60

Intraoperative imaging: stereotactic orthogonal x ray radiography versus intraoperative computed tomography – MRI issues?

wilhelm eisner (1), florian sohm (1)

1. neurosurgical, medical university innsbruck, austria, innsbruck, Austria

Submitter: Mr Eisner Wilhelm (AT)

Introduction: Neurosurgery and especially stereotactic procedures are imaging dependent surgical disciplines. The brain and its function are not accessible by auscultation, percussion and palpation.

Methods: After Wilhelm Röntgens detection of the x-rays it was possible to implement anatomical drawings in form of atlases into the internal bony boundaries of a patient skull by orthogonal x-ray radiography. Further information was gained by pneumencephalography, ventriculography and angiography. The mid seventies brought us computed tomography and the eighties magnet resonance tomography. Functional imaging by positron emission tomography and magnet resonance tomography payed tribute to the individual functional distribution. Diffusion tensor imaging added the tractography and completed imaging up to now so far. During end of the nineties ventriculography was replaced by mri measurements. Still many stereotaxy centers perform x-ray radiography before and after surgery in the operating room to prove surgery being performed as originally planned. The intraoperative x-ray radiography devices are out of production since mid nineties and have to be custom made from replacement parts for each order or intraoperative installation. The price for a new device is more than 300 kilo €. The price is in the range of an intraoperative computed tomography device with a larger gantry opening because of surgical reasons. A possible higher price for an intraoperative computed tomography is easily reimbursed by use of the instalment for other indications like vascular and minimal invasive spinal surgery. We want to compare intraoperative x-ray radiography and computed tomography in its content on information for the surgeon and the patient. Further we will discuss issues with magnet resonance tomography.

Results: Intraoperative x-ray imaging delivers a quick and easy performed distribution of instruments, electrodes, catheters and implants in the three x-y-z planes in relation to a stereotactic frame affixed to a patient skull. Information on soft tissue and vascularisation of the brain are not accessible. Bleedings or haemorrhages are invisible and not direct detectable. Indirect signs for a haemorrhagia are distortion or displacement of the implant. Than it would be wise to perform a computed tomography to see what happened. Than you have to go back to the surgical theatre to react on what happened. All that can easily be avoided by bringing the computer tomography into the operation room and not buying an intraoperative x-ray device. The content on information is far beyond stereotactic radiography. Patient safety can be improved and the examination is performed in less than 5 minutes proven by more than 1000 patients.

Conclusion: Intraoperative computed tomography became the new standard in stereotactic imaging and in neurosurgery.

#74

Localization of Deep Brain Stimulation Targets by Deterministic Tractography Using an Available Navigation System

Juan A. Barcia (1), Josue Avecillas-Chasin (1), Fernando Alonso-Frech (2), Olga Parras (3)

1. Neurosurgery, Hospital clinico San Carlos, Madrid, Spain

2. Neurology, Hospital clinico San Carlos, Madrid, Spain

3. Medicine, Universidad Complutense de Madrid, Madrid, Spain

Introduction: Recent advances in imaging permit radiologic identification of target structures for deep brain stimulation. However, these methods cannot detect the internal subdivision, and thus cannot determine the appropriate DBS target “bull’s eyes” located within those subdivisions. The objective is to provide a straightforward method for identification of bull’s eyes within DBS targets using a widely available navigation system.

Methods: We used T1 and T2 weighted images, FLAIR sequence, and DTI of nine patients operated for DBS in our center. Using the StealthViz® Software and anatomical landmarks from MRI studies, we segmented the targeted deep structures (subcortical structures of the basal ganglia and thalamus) and the anatomically identifiable areas to which these targets were connected (at the cortex or other subcortical structures). Through deterministic tractography (DTI-DT), we generated fiber tracts from the projection areas. By identifying their “intersections” with the subcortical targets, we obtained regions coincident with internal subdivisions of DBS targets

Results: We were able to identify bull’s eyes coincident with the motor part of the subthalamic nucleus (STN) and ventral intermediate nucleus (VIM). We clinically tested the results and found that the most clinically effective combinations of electrode contacts were very closely related to different internal subdivisions of the DBS targets, obtained with our newly described method. Statistical data analysis was done with a Wilcoxon signed-rank test that was used to compare the medians of the distances, with $p < .05$ considered statistically significant

Conclusion: Despite the limitations of deterministic tractography, our present results show that this novel method permits identification of bull’s eyes within the internal subdivisions of targets for DBS.

#79

Identification of the anatomic networks of Wakefulness & Awareness for the treatment of patients with disorders of Consciousness

Stefanos Korfias (1), Marios Themistocleous (1), Efthymios Angelakis (2), George Stranjalis (3), Damianos Sakas (1)

1. Neurosurgery, University of Athens, Evangelismos Hospital, Athens, Greece

2. Neuro-psychology, University of Athens, Athens, Greece

3. Neurosurgery, University of Athens, Evangelismos Hospital, Athens, Greece

Submitter: Mr KORFIAS STEFANOS (GR)

Objectives: To present the brain anatomic circuits of Consciousness. Damage of these brain areas may result in Persistent Vegetative State (PVS) or Minimally Conscious State (MCS).

Methods: We reviewed the available literature and recorded all the brain nuclei and networks participating in consciousness (wakefulness & awareness).

Results: Wakefulness is controlled by certain brain areas located in the brain stem, hypothalamus, thalamus and basal forebrain.

The brainstem Ascending Reticular Activating System (ARAS) projects to the thalamocortical system achieving arousal in combination with locus coeruleus, raphe nuclei, and ventral periaqueductal grey matter.

Anterior hypothalamus suppresses wakefulness through the suprachiasmatic nucleus and the ventrolateral preoptic nucleus, while posterior and lateral hypothalamus promotes wakefulness through the tubero-mammillary nucleus.

Thalamocortical neurons from the non-specific thalamic nuclei can promote or suppress arousal depending on their electrophysiological state.

Substantia innominata with adjacent basal forebrain areas can also promote or impair wakefulness.

Awareness is controlled in brain areas located in the cortex. Internal – self-awareness is controlled by midline cortical areas (precuneus, anterior, posterior cingulate, mesiofrontal parahippocampal areas), while external – environmental awareness is controlled by lateral fronto-parietal cortical areas.

Conclusion: The recognition of certain anatomical areas as modulators of wakefulness and awareness could offer new targets for Functional Neurosurgery in patients with coma, PVS or MCS.

#88

Ultra-high resolution ex vivo connectivity and parcellation of the human subthalamic nucleus

Birgit Plantinga (1), Alard Roebroek (2), Matteo Bastiani (2), Valentin Kemper (2), Mark Kuijf (3), Kâmil Uludağ (2), Bart ter Haar Romeny (4), Yasin Temel (5)

1. Department of neuroscience, Maastricht University, Maastricht, Netherlands

2. Department of cognitive neuroscience, Maastricht University, Maastricht, Netherlands

3. Department of neurology, Maastricht University Medical Center, Maastricht, Netherlands

4. Department of biomedical image analysis, Eindhoven University of Technology, Eindhoven, Netherlands

5. Department of neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

Submitter: Melle Plantinga Birgit (NL)

Introduction: The subthalamic nucleus is a key component of the basal ganglia, and is involved in motor, limbic and associative processes. Deep brain stimulation of the subthalamic nucleus is used to treat disorders associated with basal ganglia function such as Parkinson's disease and obsessive compulsive disorder. With the existing routine imaging modalities, it is not possible to visualize motor and limbic target areas within the subthalamic nucleus.

Advanced MR imaging techniques, such as functional MRI and diffusion MRI can make it possible to investigate this subdivision. However, due to its small nature (the longest axis is approximately 5.9-11.5 mm), the limited scanning time, and the typical field strength of clinical MR systems, the subthalamic nucleus often only comprises a few voxels on these images, which impedes detailed sub-millimeter analyses.

This study aims to investigate the structural connectivity and parcellation of the subthalamic nucleus at a sub-millimeter resolution with the aid of an ultra-high field MR system.

Methods: A unilateral human post mortem specimen including the subthalamic nucleus, the substantia nigra, the red nucleus, and the internal and external globus pallidus was obtained from the department of anatomy and embryology of Maastricht University (The Netherlands). Although originally kept on formalin, it was scanned in PBS with a 7T MRI scanner (Magnetom 7T, Siemens, Erlangen, Germany). The scan protocol consisted of two scans: a) 0.3 mm isotropic voxels gradient echo (GE) imaging with an echo time (TE) of 11 ms and a repetition time (TR) of 37 ms, and b) 0.5 mm isotropic voxels diffusion weighted imaging (TE = 60 ms and TR = 500 ms) with 60 directions with a b-value of 2800 s/mm² and an additional 8 b₀-volumes, with a scan time of over 65 hours. The subthalamic nucleus was manually delineated from the GE image using ITK-SNAP. Eddy current and motion correction of the diffusion weighted images was performed with FSL's eddy_correct. Finally, the MRtrix package was used to perform diffusion tensor based deterministic fiber tracking from the subthalamic nucleus to obtain its connections to other structures and derive a connectivity map.

Results: The subthalamic nucleus could clearly be separated from the substantia nigra on the GE image. The main fiber direction within the subthalamic nucleus was from posterolateral to ventromedial. A number of pathways could be distinguished emerging from the subthalamic nucleus. One pathway, probably belonging to the ansa lenticularis, started in the subthalamic nucleus passing around the internal capsule anteromedially to both the internal and external globus pallidus. Other fibers followed the adjacent internal capsule into superior direction. Further analysis of these pathways showed that the connection between the subthalamic nucleus and the globus pallidus internus emerged from the anteromedial side of the subthalamic nucleus, whereas the connections aligning with the internal capsule fibers, originated from the dorsolateral part of the subthalamic nucleus.

Conclusion: We have shown that scanning a post-mortem tissue sample with an ultra-high field MR system equipped with high amplitude gradients and exploiting a long scanning time allows for identification of the main fiber tracts connecting sub-cortical structures at a sub-millimeter resolution. The results of this study show a segregation of the origin of fibers running from the subthalamic nucleus to the connected structures linked to motor and limbic functions. This segregation of structural connectivity and subthalamic anatomy using ultra-high field imaging techniques may aid in better clinical pre-operative targeting of DBS patients.

#105

3-D Position of STN in T2 weighted MR images compared to Stereotactic Atlases for functional neurosurgery planning

Erich Talamoni Fonoff (1), William Omar Contreras Lopez (2), Paul Rodrigo Reis (1), Eduardo Alho (1), Jairo Angelos (3), Jessie Navarro (4), Manoel Jacobsen Teixeira (5)

1. *Functional and Stereotactic Neurosurgery, University of Sao Paulo, Sao Paulo, Brazil*

2. *Functional and Stereotactic Department, University of Sao Paulo, Sao Paulo, Brazil*

3. *Functional and Stereotactic Department, University of Sao Paulo School of Medicine, Sao Paulo, Brazil*

4. *Physiology, Functional Neurosurgery, University of Sao Paulo, Sao Paulo, Brazil*

5. *Neurosurgery, University of Sao paulo, Sao Paulo, Brazil*

Submitter: Mr Contreras Lopez William Omar (CO)

Introduction: Currently there are several standard atlases available that are used to localize the STN in functional MRI studies and clinical procedures such as deep brain stimulation (DBS). However, current atlases are based on low sample sizes and restricted age ranges (Schaltenbrand and Wahren, 1977, Morel 2007), and hence the use of these atlases effectively ignores substantially individual differences in brain structural and the changes associated with aging. Here we aimed to compare the position and the volumen of STN observed in the T2 weighted MR images in comparison the same structure in the Schaltenbrand and Morel atlases.

Methods: Magnetic resonance images of ten parkinson patients who underwent bilateral STN DBS implant were fused through linear warping technique into the same stereotactic space of the anatomical 3D reconstruction of STN outline based in the Schaltenbrand & Wahren (1977) and Morel (2007) atlases. The STN 3D reconstruction was performed in each of the atlas plataforms and also based in the hypointense region in the T2 MRI according to Nakajima et al (2011) that represents the position of STN in the same stereotactic space.

Results: We found that the position of STN in the Schaltenbrand Atlas tend to be more lateral and compared to the MRI hypointense region (STN representaion in T2 MRI). While the STN reconstruction in the Morel Atlas was highly coincident with the STN representation in the MRI in slight medial position. The distance from midline of the STN centroid in the SW Atlas was in average 11.3SD0.2mm, in the Morel Atlas was 9.60SD0.23mm and in the MRI STN centroid was 10.8SD0.88mm.

Conclusion: Our series found Morel atlas to be more accurate in relation to patient image T2 modified series than Schaltenbrand in which was found more lateral. The Present data suggests that MRI-based target is apparently more individual based, as expected, that are the atlases even when conformational warping is performed.

#148

Is there still a need for Gadolinium in stereotactic DBS planning procedures ? – The value of susceptibility weighted MRI.

Frank Hertel (1), Andreas Husch (1), Florian Bernard (1), Georges Doods (2), Peter Gemmar (3)

1. Neurosurgery, Neurosurgery CH Luxembourg, Luxembourg, Luxembourg

2. Neuroradiology, CH Luxembourg, Luxembourg, Luxembourg

3. Computer Sciences, University of Applied Sciences, Trier, Germany

Submitter: Mr Hertel Frank (LU)

Introduction: Gadolinium enhanced T1 weighted, as well as T2 weighted MRI sequences are currently most widely used for the planning of Deep Brain Stimulation (DBS) procedures . Within the recent years, highly susceptibility weighted sequences (SWI) have been introduced to image especially neurovascular structures, as well as brain areas with high ferrum content.

Methods: We performed DBS trajectory planning, as well as target definition for DBS procedures (STN, VIM) with standard Gd enhanced T1 weighted and with (for STN definition) T2 weighted MRI in 20 data sets leading to data from 100 trajectories and 40 STN targetings.

Afterwards, we matched the SWI sequences @ an S7 planning station (Medtronic, Minneapolis, USA) and analyzed the trajectories again in means of potential neurovascular conflicts due to SWI imaging and in means of inter- and intraindividual differences of STN anatomy.

Results: In 53 out of 100 planned trajectories (planned means negative for neurovascular conflict in Gd-T1), we saw a neurovascular conflict in SWI. On the other hand, all potential conflicts visible in SWI, as well. SWI furthermore showed the delineation of STN much clearer, than T2. The interindividual and intraindividual heterogeneity of STN was significant and much better visible in SWI.

Conclusion: Keeping in mind, that it was demonstrated, that the spatial accuracy of SWI is similar (or even superior) to T1 and T2, together with the results of our studies lead us to the question, if SWI weighted MRI alone, may be sufficient and more effective for DBS planning (target, as well as trajectory) as those latter ones. Furthermore, contrast enhancement would not be required for SWI imaging.

#185

MRI methods to localise the ventral intermediate nucleus of the thalamus: structural imaging and connectivity data

Adrian Zammit (1), Harith Akram (2), Mark White (3), Enrico De Vita (3), Ludvic Zrinzo (2)

1. *Institute of Neurology, University College London, London, United Kingdom*

2. *Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, London, United Kingdom*

3. *Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, London, United Kingdom*

Submitter: Mr Zammit Adrian (GB)

Introduction: Stimulation of the ventro-intermediate (Vim) nucleus of the thalamus was primarily developed into a tremor-specific target and has successfully retained this role in providing symptomatic improvement in cases refractory to medical management. Targeting of the Vim nucleus for deep brain stimulation (DBS) currently depends on population-based, atlas-derived stereotactic coordinates. Recent advances in neuroimaging modalities have opened the possibility of in vivo target identification. The study was designed as a preliminary investigation to evaluate the role of diffusion-tensor imaging (DTI) based probabilistic tractographic segmentation of the thalamus and high-field structural magnetic resonance imaging (MRI) in DBS targeting.

Methods: Two healthy volunteers and two patients scheduled for Vim DBS had diffusion-weighted imaging and high-field structural imaging on a 3T MRI scanner. Connectivity-dependent thalamic segmentations were derived from a 128-direction DTI with a voxel size of 1.5mm³ using a previously published technique. The current understanding of thalamic neuroanatomy suggests that the Vim provides the main efferent projection to the Brodmann Area (BA) 4, thus allowing identification of this nucleus on segmentation. A structural T1-weighted Turbo Inversion Recovery sequence for identification of the putative Vim was also performed. Coordinates of sites of interest within connectivity maps and structural imaging were then identified. The relationship between the coordinates, as well as traditional stereotactic-atlas coordinates, was then studied. DBS lead locations in the post-operative patients were then acquired and compared to the previous coordinates.

Results: A substantial inter-individual variability was demonstrated in the thalamic maps with peak connectivity to BA4 and BA6. The putative Vim on 3T-structural MRI, central coordinate of the map to BA4 and atlas-derived coordinates demonstrated a tendency to co-localise. In contrast to accepted notions of Vim connectivity and DBS targeting, DBS contacts were seen to co-localise with peak connectivity maps to BA6 (centre-to-centre distance of 0.66-2.33mm), substantially more anterior to the BA4 map (centre-to-centre distance of 4.00-5.37mm).

Conclusion: This study provides additional evidence to support further research on the implementation of both imaging strategies, in particular connectivity-based thalamic segmentation, for patient-specific DBS targeting. It also provides new mechanistic insights on the effect of DBS on thalamocortical networks.

#190

Evaluating the extent of CT to MRI fusion error in deep brain stimulation patients

David Kis (1), Laszlo Entz (2), Laszlo Halasz (2), Adrienn Mate (1), Peter Klivenyi (3), Pal Barzo (4), Lorand Eross (2)
 1. *Department of Neurosurgery, Functional Neurosurgery and Brain Mapping Group, University of Szeged, Szeged, Hungary*
 2. *Department of Functional Neurosurgery, National Institute of Clinical Neuroscience, Budapest, Hungary*
 3. *Department of Neurology, University of Szeged, Szeged, Hungary*
 4. *Department of Neurosurgery, University of Szeged, Szeged, Hungary*

Submitter: Mr Kis David (HU)

Introduction: Fusion of the postoperative CT to the preoperative MRI images is a frequently used method to define the location of deep brain stimulation (DBS) electrodes. However, fusion error can produce unreliable results. The reliability of CT to MRI fusion hasn't been systematically verified yet. In this study we aimed to define the mean fusion error of CT to MRI co-registration and provide reliability data using postoperative imaging and analysis methods after DBS surgery.

Methods: Five patients who underwent bilateral DBS implantation were enrolled in the study. All of them had postoperative CT (axial 1 mm slices, no gap, no gentry tilt) and MRI (axial 3D T1, 1x1x1 mm voxel size, 1.5 T scanner) images. The FSL's (Oxford University) FLIRT tool was used to register the CT images to the MRI native space (linear registration, 6 degrees of freedom, mutual information). The registration was repeated 10 times in each patient to account for the reliability of the algorithm. To exclude the metal artifact both on the CT and MRI images, one (center) voxel was marked by using intensity-based center of gravity in each axial slice at the level of each contact. Finally we compared the overlap and distance of the electrodes on the CT and MRI images.

Results: We found overlapping electrodes on the CT and MRI images on 37±16% on the left and 43±19% on the right side of the axial slices. In the remaining slices, the electrodes were in the neighboring (next closest ~ 1mm) voxels on the CT and MRI images.

Conclusion: According to our results, the error of CT to MRI fusion is between 0-1 mm. Therefore we believe that precise intermodal co-registration can reliably be used to define the position of the DBS electrodes on postoperative imaging. However, different CT and MRI imaging parameters can cause different fusion error, therefore similar verification of each centers' individual methods should be encouraged.

#249

SIMULTANEOUSLY STEREOTACTIC FIBRINOLYTIC EVACUATION OF DEEP SEATED INTRASEREBRAL AND INTRAVENTRICULAR HEMORRHAGES

Selhan Karadereler (1), Burcu Goker (2), Ozlem Tuncer (3), Ebru Altindag (4)

1. Neurosurgery, Istanbul florence nightingale hospital, Istanbul, Turkey

2. Neurosurgery, Bilim university, Istanbul, Turkey

3. Neurology, Bilim university, Istanbul, Turkey

4. Neurology, Istanbul florence nightingale hospital, Istanbul, Turkey

Introduction: Intraventricular hemorrhage (IVH) secondary to intracerebral hemorrhage (ICH) is associated with high mortality and morbidity. The use of fibrinolytic agents to treat IVH or ICH has previously been reported in clinical trials and retrospective reports suggest clinically significant benefits in terms of reduced mortality. Concurrently evacuation both of these hemorrhages is not previously reported in the literature. In this study, we reported simultaneously fibrinolytic evacuation both of IVH and ICH with a single stereotactic catheter passing from ICH and advancing to IVH.

Methods: Five patients (3 males and 2 females, with an average age of 63 years [range 41-72 years]) with IVH and ICH volume <20 mL were treated. Patients with larger ICH or neurological deterioration underwent craniotomy, image-guided keyhole craniotomy, hemicraniectomy or mechanical hematoma aspiration. Initial neurological status of patients was evaluated with Glasgow Coma Score (GCS) and modified Rankin Scale (mRS). Besides to the daily neurological following, GCS and mRS were determined at 2nd, 3rd, 7th days of treatment. Extended Glasgow Outcome Scale (GOSE) and mRS were evaluated at discharge and 6th month of following.

Surgical procedure: A frame based three-dimensional cranial computerised tomography (CT) was achieved. A trajectory passed through ICH and reached to IVH was determined. It was careful not to pass eloquent area. A ventricular catheter was inserted to target in this trajectory via a suitable bur hole with Leksell frame (Elekta AB, Stockholm, Sweden). The holed part of catheter (3 cm) was placed to the both of ICH and IVH. Recombinant tissue plasminogen activator (r-tPA) (Actilyse, Boehringer Ingelheim, Germany) was given to hematoma and this 2 mg r-tPA dosage was repeated until obtaining satisfactory hematoma evacuation and cerebrospinal liquid circulation.

Results: Total volume of ICH and IVH was decreased 31 %, 64 %, 82 % and 95 %, respectively in 12th, 24th, 48th hour and 7th day. Initial median GCS was 11,5 (between 7-13) and mRS was 3.7 (between 2-5). Median GOSE was 5.75 and outcome mRS was 2.75. In follow up examination at 6th month, median GOSE was 6.75 and mRS was 1.

Conclusion: Concurrent stereotactic fibrinolytic evacuation of IVH and ICH significantly accelerates resolution of total hemorrhage volume. Administration of r-tPA to ICH and IVH seems safe and effective in lysis of hematoma and may, therefore, improve outcome.

#275

Neuroanatomical alterations in transgenic rat model of Huntington's disease; detectable by conventional histology but not with ultra high-field MRI

Ali Jahanshahi^{1,2,4}, Joao Casaca-Carreira^{1,4}, Rinske Vlamings^{1,4}, Birgit Plantinga^{1,3}, Sarah Heschem^{1,4} and Yasin Temel^{1,2,4}

Departments of ¹Neuroscience and ²Neurosurgery, Maastricht University Medical Center, Maastricht, the Netherlands

³ *Eindhoven Technical University*

³European Graduate School of Neuroscience (EURON)

Objectives: To further characterize the process of neurodegeneration associated with early, middle and late disease phases in tgHD rats and to examine the sensitivity and reliability of the MRI technique in detecting volumetric changes, we conducted a longitudinal histological and ultra high-field MRI study.

Methods: We investigated the volumetric changes in the striatum, lateral ventricle and the neocortex of tgHD rats at 9, 12 and 18-months of age.

Results: Stereological analysis did not show a statistically significant neuronal cell loss in the striatum at early stage of the disease; however, it revealed a significant reduction in striatal cells volume. Moreover, we observed a substantial atrophy in the striatum; enlarged ventricular volume and a thinning of the neocortex in the brains of tgHD rats only at late disease phase in comparison to the wild type (WT) littermates. Surprisingly, 7-Tesla MR scans did not show any detectable volumetric change between tgHD and WT rats in the brain at 9, 12 and 18 months old of age, despite the volumetric changes observed after histological processing of brain section, suggesting that MRI might not be a suitable tool to detect the volumetric changes in the rodents.

Conclusion: Our findings show that neuronal shrinkage precedes the striatal atrophy in tgHD rats. Moreover, similar to human HD, the manifestation of striatal atrophy appears prior to cortical thinning in tgHD rats.

2.7 Neuromonitoring

#93

AWAKE NEUROLOGICAL MONITORING WITH SUPRASELECTIVE PROPOFOL INJECTION DURING EMBOLIZATION OF AVM IN ELOQUENT AREA

Hendrik Fransen (1), David Colle (2), Bonny Noens (2), Erik Robert (3), Giovanni Alessi (2), Henry Colle (2)

1. Neuroradiology, AZ St Lucas, Ghent, Belgium

2. Neurosurgery, AZ St Lucas, Ghent, Belgium

3. Neurolinguistics, AZ St Lucas, Ghent, Belgium

Introduction: In patients presenting with an AVM in an eloquent brain area, embolization under general anesthesia can be hazardous; neurophysiological monitoring with SEP or MEP can be useful but remains cumbersome and time-consuming, and allows only testing of sensory or motor pathways. Awake clinical neurological monitoring of sensori-motor and linguistic functions, and of visual fields can afford safe evaluation prior to embolization of AVM's in eloquent areas.

Methods: A 15 y old male patient presented with headache, without neurological deficit; a left occipital AVM was diagnosed. During the neuro-interventional procedure, supraselective catheterization was performed of the afferent artery under general anesthesia, which was disrupted for awake neurological evaluation: clinical motor testing, interactive linguistic evaluation with I-pad and visual field testing with an O.R. dedicated device were performed, first base-line, then during Propofol injection ; no deficit appeared, general anesthesia was re-applied and embolization with Onyx° performed.

Results: The patient underwent embolization of the AVM without any post-procedural neurological deficit.

Conclusion: Embolization of AVM under general anesthesia, after awake monitoring of different neurological functions during supraselective arterial injection with anesthesiological agents reveals to be a reliable and safe method to avoid possible post-embolization deficits.

#160

Subcortical stimulation guided stereotactic biopsy for tumors in the posterior insular area

David Colle (1), Giovanni Alessi (1), Henry Colle (2), Bob D'Haen (2), Bonny Noens (2), Chris van der Linden (3), Erik Robert (4)

1. *Department of Neurosurgery, AZ St Lucas, Gent, Belgium*

2. *Department of Neurosurgery, AZ St Lucas Gent, Gent, Belgium*

3. *Department of IO Neurophysiology, AZ St Lucas Gent, Gent, Belgium*

4. *Department of Neurolinguistics, AZ St Lucas Gent, Gent, Belgium*

Introduction: For non-resectable tumours located at the posterior part of the insula, near the arcuate fasciculus, blind biopsy within the fascicle can be hazardous with risk of harming functional tissue. Subcortical stimulation with the classical macro-electrodes used for DBS could provide safety, excluding functionality of the area to be biopsied.

Methods: Two patients, presenting with non-resectable posterior insular tumours near the arcuate fascicle on DTI-FT, underwent biopsy after introduction of a macro- electrode as used for DBS, the navigation system providing an optimal approach (one frontal precoronal, one parietal) between the sulci and medial cerebral artery branches in the area . Stimulation was performed with motor and language testing, at the parameters used during awake tumour resection in eloquent areas). Counting, object naming, and particularly sentence repetition were tested at different depths; no speech arrest or other language disturbances occurred, the stimulation needle was withdrawn and replaced by the Nashold biopsy needle in the same trajectory. During biopsy, the language testing was continued, and prolonged some minutes after tissue removal.

Results: Both biopsies revealed tumoural tissue, compatible with high grade glioma WHO IV, glioblastoma multiforme, and radio-chemotherapy according to Stupp was started.

Conclusion: Biopsies in highly eloquent areas with difficult approach can be safely realized using prior subcortical stimulation and motor-language testing with a DBS-electrode ; this indicates the need for a biopsy needle with insulated tip, allowing stimulation with the same probe, and avoiding the need of two trajectories.

2.8 Neuro-oncology

#61

Is it possible to remove subcortically located space occupying lesion in the sensory motor strip with motor function improvement?

Wilhelm Eisner (1), Florian Sohm (1), Miriam Mulino (1), Thomas Fiegele (1)
 1. Neurosurgical, Medical University Innsbruck, Innsbruck, Austria

Introduction: Subcortical lesions in the sensorimotor strip are often considered to be inoperable. Functional magnet resonance tomography has proven to show motor function distribution but it is not able to exhibit particular motor function immediately above and around a circumscribed lesion. Electrophysiological methods like the phase reversal phenomenon of the primary cortical response following median nerve stimulation in the central sulcus is neither able to give neurosurgeons information of the local motor function distribution. The purpose of this study was to evaluate the practical value of a combined approach aided by frame based or frameless stereotactically guided surgery under electrophysiological control by direct cortical and subcortical stimulation.

Methods: In a prospective study on 21 patients, space occupying lesions in the sensorimotor area were removed using the Leksell stereotactic frame (11 patients) or Surgiscope® robotic navigation system (10 patients) and the Nicolet Viking IV® electrophysiological system utilizing direct cortical bipolar stimulation with cortical EEG recordings for identification of epileptic after-discharge.

Results: Precise tumour localisation was achieved by both targeting systems and the information on the patient's cortical motor distribution obtained by bipolar cortical stimulation led to postoperative improvement in motor function in all patients by respecting and not disrupting the course of motor fibre tracts. 11 patients out of 21 showed postoperatively motor improvement and 9 were equal to the preoperative neurological state. Only one patient had postoperatively a new drop foot as the only deterioration in all patients. He exhibited preoperatively a hip bending weakness which resolved postoperatively. 15 of the patients had focal, defined pathologies (7 metastases; 2 cavernomas; 5 granulomas, 1 vascular malformation) which were removed radically.

Conclusion: Due to the implementation of the two described technologies, surgery of lesions in the subcortical sensory-motor region can be performed with greater confidence and less motor deficits in the hand of experienced neurosurgeons.

#78

Post operative T2 hyperintensity in peri resection margin following total macroscopic resection of Low Grade Gliomatous tumours are not a reliable marker residual disease or long term adverse outcome.

Huai Hao Khor (1), Surajit Basu (1)

1. Neurosurgery, Queen's Medical Centre, Nottingham, United Kingdom

Introduction: Post operative MRI examination is an established method of assessment of completeness of resection of intrinsic brain tumours. While T1 contrast MRI sequences can depict enhancing tumour residue whereas for non enhancing low grade tumours, T2 hyperintensity is often considered relevant. However peri operative retraction of surrounding brain, blood flow changes can cause changes in T2 signal from the surrounding tissue which may get misinterpreted as residual disease. We undertook this audit in a homogenous group of patients undergoing awake craniotomy for hemispheric low grade tumours, undertaken by same surgical team employing uniform surgical technique to study long term evolution of these T2 changes and its implication in clinical outcome.

Methods: This is a retrospective analysis of post operative MRI of patients who had awake craniotomies undertaken between 2007-2014. Patients were identified through operative department records, while radiological and clinical data were obtained through the hospital's electronic patient records and image system. A correlative analysis was done between immediate post-operative T2 changes and long term tumour progression.

Results: 37 patients underwent awake craniotomy for radiological low grade glial series lesions. Average age of patients was 41.1 yrs (range 21-79). 6 patients have died (average survival 2.69 years, range 1-84 months) due to tumour progression. 5 of these had initial diagnosis of grade 3 tumour or above; 32(85%) patients have survived the survey period (2.38 years, range 1-72 months). On MRI all patients had post-operative T2 hyperintensity around the resection margins. The T2 hyperintensity persisted or increased in only 6 patients (19%). This was correlated with a peri-operative decision to sub-totally resect and subsequent tumour progression. In other 31 patients the T2 changes either reduced or remained static through the follow up period. Histology of these patients showed 4 had grade 2, 22 had grade 3, and 5 had grade 4 tumour.

Conclusion: T2 changes in peri-resection brain parenchyma following a macroscopic complete resection of low grade tumours is not a reliable marker of residual disease. In 80% of our cases, such changes remained static or reduced in subsequent imaging.

#100

Comparison of efficacy, safety and advantages between frameless nonfiducial and standard frame-based brain biopsy

Miltiadis Georgiopoulos (1), Sotirios Raftopoulos (1), Aikaterini Apostolopoulou (1), Constantine Constantoyannis (1)
 1. Functional Neurosurgery Unit, Department of Neurosurgery, Faculty of Medicine, University of Patras, Patras, Greece

Introduction: Biopsies of cerebral lesions can be performed without the classic cumbersome stereotactic frames or fiducials, using the “frameless nonfiducial” stereotactic method, guided by an intraoperative navigation system. The objective of the present study is the comparison of efficacy, safety and advantages of the above method in biopsies of intracranial lesions to the standard stereotactic technique using the Cosman-Roberts-Wells frame.

Methods: In this prospective double-blind (for patients and the evaluator of statistics) study 28 patients, 28-82 years old (mean: 59.9), were operated with the standard stereotactic technique and 28 patients, 34-76 years old (mean: 57.8), with the “frameless nonfiducial” stereotactic method guided by the intraoperative navigation system “StealthStation® S7™” (Medtronic Navigation, USA).

Results: In 4 cases (14,3%) of the standard method and 3 cases (10,7%) of the frameless method no diagnosis was established. Postoperative complications was recorded in one patient (3,6%) in each group. The mean duration of postoperative hospitalization was 3.3 days (SD:3.7, SE:0.8) following the frame-based stereotactic biopsy and 2.3 days (SD:2.1 SE:0.4) after the frameless biopsy, no statistically significant difference. The mean duration of the technique was 114,8min (SD:19,2, SE:6,1) for the “standard group” and 79,1min (SD:22,7, SE:8,0) for the “frameless group”, a statistically significant difference.

Conclusion: The method of frameless stereotactic biopsy guided by intraoperative navigation is equally efficacious and safe compared to the standard frame-based, while its duration is shorter and it is friendlier to the surgeon.

#111

Interstitial brachytherapy with iodine-125 seeds for low grade brain stem gliomas in adults: diagnostic and therapeutic intervention in a one-step procedure.

William Omar Contreras Lopez (1), Michael Trippel (2), Soroush Doostkam (3), Thomas Reithmeier (4)

1. *Functional and Stereotactic Department, University of Sao Paulo, Sao Paulo, Brazil*

2. *Functional and Stereotactic Neurosurgery, Freiburg University, Freiburg, Germany*

3. *Pathology, Freiburg University, Freiburg, Germany*

4. *Neurosurgery, Munchen University, Freiburg, Germany*

Objective: To report on iodine-125 (I125) interstitial irradiation in the treatment of low grade brain stem gliomas in adults.

Methods: Ten patients with well-circumscribed lesions of the brainstem and histological confirmation of low grade glioma treated with stereotactically implanted I-125 seed in our department between 1995 and 2012 were retrospectively analyzed.

Results: In 9 patients the lesion was treated with one I-125 seed and in one patient, 2 spatial separated lesions were implanted, therefore a total of 11 I-125 seeds were implanted. The mean volume of the 11 lesions was 2.76 ml (range: 0.5-7.2 ml), mean activity of the seeds was 6.23 mCi (range: 1.5-11.1 mCi), mean duration of irradiation was 28.5 days (range: 21-41 days) and mean effective dose rate was 9.16 cGy/h (range: 6.2-12 cGy/h). The 30 days perioperative morbidity and mortality rate was 0%. Median follow up was 72.5 month (range 5-168 months). Six of ten patients were free of progression until last follow up.

Conclusion: In our experience at the University Clinic in Freiburg Germany, interstitial radiosurgery based on MRI is a safe and effective method to diagnose and treat low grade gliomas of the brain stem. Furthermore randomized studies are needed to confirm the therapeutic impact of this method in comparison to external beam radiation of brain stem gliomas.

#121

Is there still a place for stereotactic brachytherapy for brain tumors in modern neuro-oncology?

List of authors missing

Submitter: Mr Ruge Maximilian (DE)

Introduction: Stereotactic implantation of irradiation sources (so called stereotactic brachytherapy (SBT)) has been applied for intrinsic brain tumors and metastases for more than four decades in numerous patients. The majority of studies reported about the application of high-dose rate Iodine-125 implants (40–70cGy/h) for high-grade gliomas, including two prospective randomized trials, which compared standard treatment \pm SBT. This approach, however, was associated with high incidence of radiation induced adverse effects requiring repeated surgery and failed to proof any significant oncological benefit as compared to standard treatment regiments. Another approach using SBT was the application of low-dose rate implants (3–8cGy/h) for slow growing low-grade gliomas or brain metastases which demonstrated in several very recent publications to be associated with only little permanent deficits and almost an absence of radiation induced necrosis.

Methods: SBT represents a highly localized treatment option for well circumscribed tumors (≤ 4 cm) and aims as well as micro-neurosurgical resection towards the devitalisation/removal of the dense (visible) portion of tumor cells by delivering a lethal irradiation dose (≥ 200 Gy in the vicinity of the implanted source) from within the tumor while optimally sparing surrounding tissue.

Results: This makes SBT as minimal invasive and safe technique highly attractive, especially for inoperable lesions in highly eloquent locations. Furthermore, SBT can be repeated in case of local/regional recurrence and does not hinder or limit the application of EBRT. Even though class I evidence is yet lacking, recent available data for low grade gliomas, metastases and other rare CNS tumors demonstrate that progression free-and overall-survival is well comparable to this after microsurgical (complete) resection or stereotactic radiosurgery. Local tumor response is at least as effective as after EBRT or chemotherapy.

Conclusion: SBT still represents as one of the oldest neurosurgical and highly sophisticated stereotactic technique a strictly local neuro-oncological treatment option for selected patient populations deserving further attention.

#245

Technique and planning software for stereotactic brainstem and basal ganglia biopsies

István Valálik (1), Ferenc Pongracz (1), András Csókay (2)

1. Department of Neurosurgery, St. John's Hospital, Budapest, Hungary

2. Department of Neurosurgery, BAZ County and Teaching Hospital, Budapest, Hungary

Introduction: In order to minimise interventional invasiveness in patients with basal ganglia and brainstem tumours, it is crucial to define the histological type of the different cerebral lesions. Although a better quality of MR imaging with new sequences has allowed a higher correlation with histological results, the presence of bias is still high.

Methods: With high resolution CT or MR techniques stereotactic targeting provides a sample of tissue even from a lesion with a size of 5 mm. Basal ganglia and brainstem as eloquent regions of the brain require special issues in the technique. In order to avoid bleeding as the most dangerous complication of the intervention, the positions of serial biopsy and tissue volume need to be carefully controlled. Specially designed biopsy module of Vister-3D stereotactic planning software with CT-MR fusion is going to be presented in the lecture. In the procedures Riechert-Mundinger and MHT stereotactic systems were used. In spite of using aspiration or spiral biopsy needles in our practice we use micro-rongeour with a 1.2-mm size. The small sample size is a great challenge for neuropathology in aspects of handling during not only the block and slice preparation but also the evaluation procedure. Preoperative management, contrast enhanced CT guidance, patient positioning and follow-up are also going to be presented.

Results: 48 cases will be presented including paediatric cases. Rare complications were asymptomatic and symptomatic bleeding. The proportion of negative results is 2%, repeated procedure has been performed in 1 case.

Conclusion: Stereotactic biopsy in the region of basal ganglia and brainstem with special technique can be performed safely in both adult and paediatric cases and it appears to allow us to redefine further therapeutic strategies.

2.9 Neurotransplantation

#110

Clinical neurotransplantation protocol for Huntington's and Parkinson's disease.

William Omar Contreras Lopez (1), Guido Nikkhah (2), Ulf Kahlert (3), Sven Moellers (4), Mate Dobrossy (4), Jaroslaw Maciaczyk (5)

1. Functional and Stereotactic Department, University of Sao Paulo, Sao Paulo, Brazil

2. Functional Neurosurgery, Freiburg University/Erlangen University Clinic, Erlangen, Germany

3. Stereotactic and Functional Neurosurgery, Freiburg University, Freiburg, Germany

4. Molecular laboratory, Freiburg University, Freiburg, Germany

5. Neurosurgery, Freiburg University?Dusseldorf University, Dusseldorf, Germany

Introduction: The concept of transplantation of neuronal cells to treat Huntington's and Parkinson's diseases is based on the proven principle that dopaminergic and GABA-ergic progenitor neurons (from the human developing ventral mesencephalon and whole ganglionic eminence) can survive, differentiate and functionally integrate into an allogenic host brain. However, several donor and host-specific variables play a major role in the safety and outcome of this procedure. In this paper, we seek to summarize an updated neural transplantation protocol, based on our institutional experience and many years of collaboration with other neurotransplantation centers.

Methods: We present a detailed clinical neurotransplantation protocol for Parkinson's (PD) and Huntington's (HD) diseases with special emphasis in understanding the anatomical relationships of the human fetal tissue that are relevant for selection of the desired cell populations.

Results: Two detailed step-wise neurotransplantation protocols are presented, outlining strategies facilitating the avoidance of possible procedure-related complications.

Conclusion: In this paper we delineated some crucial technical factors enabling the execution of a safe and effective neural transplantation. The protocols presented here might contribute to further development of the experimental clinical neurotransplantation towards a routine therapeutic procedure.

2.10 Radiosurgery

#62

Intra-european neurosurgical communication and treatment of rare indications – an option for small countries?

Wilhelm Eisner (1), Lukas Koller (1), Florian Sohm (1), Mohamad Maarouf (2), Maximilian Ruge (3), Volker Sturm (3)

1. *neurosurgical, medical university innsbruck, austria, innsbruck, Austria*

2. *Dept. for Stereotactic and Functional Neurosurgery, Medical University Cologne, Cologne, Germany*

3. *Stereotaxy and Functional Neurosurgery, Medical University Cologne, Cologne, Germany*

Introduction: Nowadays in modern medicine, many highly specialised treatment methods are available. Because of the high costs and logistic issues, not all of them are available in every European country. Although most patients can be treated in national institutions, a small number of patients benefit from therapy which is only offered in a few specialised hospitals abroad. Even if doctors are familiar with a highly specialised method, the logistical and technical efforts are too big for working economic if there are just a few patients a year. Fifteen procedures a year are an estimated minimum in DBS, over 30 new operations a year characterizes an experienced center in DBS. In this case series we show an example of patients from the Innsbruck University Hospital, with highly specialised brain tumor conditions, where the best treatment option was the implantation of Iodine-125 Seeds, which was performed by the Stereotactic and Functional Neurosurgical Department of Cologne University Hospital.

Methods: In 15 Patients of neurosurgical department of University Hospital Innsbruck, suffering from brain tumors WHO I-IV, diagnose was saved by stereotactic biopsy, 13 in Innsbruck, 2 in Cologne. In all 15 patients indication for Iodine-125 seed implantation was set and the patients were referred to Cologne University Hospital for performing the procedure. Postoperative percutaneous irradiation (following Cologne's protocol, patients with WHO III and IV tumors) and chemotherapy was performed by Innsbruck University Hospital. One patient was treated adjuvant by proton irradiation, performed by Heidelberg University Hospital. Patient follow up was performed by Innsbruck University Hospital. The follow up MRI-Scans and neurological examination results were sent to Cologne for a joint opinion.

Results: 15 patients (11 male), median age 35 years (range 4-73), with initial diagnoses of Pilocytic Astrocytoma WHO I (n=1), Astrocytoma WHO II (n=10), Astrocytoma WHO III (n=3) and Pineoblastoma WHO IV (n=1) were treated. Median tumor volume was 9,9 ml (range 0,8-43,0 ml). In a median follow-up period of 65 months (range 3-239) 73% (n=11) patients were alive. As expected and described elsewhere before, Iodine 125 seed implantation as a first line therapy brought a benefit especially to patients with low grade gliomas in eloquent areas (Astrocytoma WHO I and II survival 82% (9 of 11 patients), median observation period 86 months (range 3-239). In high grade gliomas, patients normally only benefit for 5 half-life periods (300 days), after that high grade gliomas mostly progress (Astrocytoma WHO III and IV survival 50% (2 of 4 patients), median observation period 39 months (range 11-231).

Conclusion: It is possible to treat patients in cooperation with specialised hospitals abroad. Ofcourse, doctors have to have knowledge about specialised methods offered abroad and have them in mind as an option when treating patients. For hospitals without a specialist on a special method it can be challenging to set the indication for highly specialised methods offered abroad. So it is important to have a specialists communication.

#187

Combined approach for the management of large vestibular schwannomas: planned subtotal resection followed by Gamma Knife surgery in a series of 20 consecutive cases

Roy Thomas Daniel (1), Constantin Tuleasca (1), Mercy George (2), Louis Sciappacasse (3), Michele Zeverino (4), Raphael Maire (2), Marc Levivier (1)

1. Neurosurgery Service and Gamma Knife Center, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

2. Department of ENT, Head & Neck Surgery, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

3. Radiation Oncology Service, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

4. Institute of Radiation Physics, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Introduction: The management of large lesions of the skull base, such as vestibular schwannomas (VS) is challenging. Microsurgery remains the main treatment option. Combined approaches (planned subtotal resection followed by Gamma Knife surgery (GKS) for residual tumor long-term control) are being increasingly considered to reduce the risk of neurological deficits following complete resection. The current study aims to prospectively evaluate the safety-efficacy of combined approach in patients with large VS.

Methods: We present our experience in 20 consecutive cases. One case was lost for follow-up, due to moving to another country. Clinical and radiological data and audiograms were prospectively collected for all patients, before and after surgery, before and after GKS, at regular intervals, in dedicated case-report forms. Additionally, for GKS, dose-planning parameters were registered.

Results: Nineteen patients (6 males and 13 females) with large VS had been treated by combined approach with 22 surgeries and 21 GKS procedures. The mean age at the moment of surgery was 52 years (range 34.4-73.4). The mean presurgical diameter was 36.1 (range 26.1-45). The mean presurgical tumor volume was 15.7 cm³ (range 5 - 34.9). Three patients (15.8%) needed a second surgical intervention because of the high volume of the remnant tumor. The mean follow-up after surgery was 24.4 months (range 2-55.3). The timing of the GKS was decided on the basis of the residual tumor shape following surgery. The mean duration between surgery and GKS was 8.8 months (range 4-22.8). The mean tumor volume at the moment of GKS was 4.4 cm³ (range 0.5-12.8). The mean prescription isodose volume was 6.3 cm³ (range 0.8-15.5). The mean number of isocenters used was 20.4 (range 11-31). The mean prescription dose at the 50% isodose was 11.7 Gy (range 11-12). We did not have any major complications in our series. Postoperative status showed no functional facial nerve deficits (House-Brackmann I) (0%). Six patients with useful pre-operative hearing (GR class 1) underwent surgery with the aim to preserve cochlear nerve function; of these patients, 5 (83.3%) of them remained in GR class 1 and one (16.7%) lost hearing (GR class 5). Two patients having GR class 3 at baseline remained in the same GR class, but the tonal audiometry improved in one of them during follow-up. Eleven patients (57.8%) were in GR class 5 preoperatively; one patient improved hearing after surgery, passing to GR class 3 postoperatively. One patient, who presented with secondary trigeminal neuralgia before surgery, had transitory facial hypoesthesia following surgery. No other neurological deficits were encountered. No new neurological deficits were encountered and hearing remained stable in all patients with post-surgery preserved hearing.

Conclusion: Our data suggest that planned subtotal resection followed by GKS has an excellent clinical outcome with respect to functional preservation of cranial nerves. The goal of microsurgery for large VS experiences a shift in paradigm, from tumor excision to nerve function. As long-term results emerge from this approach, this may become a new standard of care for large VS.

2.11 Experimental studies

#22

The change of extracellular contents of striatal glutamate and GABA after high frequency stimulation of the subthalamic nucleus in 6-hydroxydopamine lesioned hemiparkinsonian rat

Chul Bum Cho (1)

1. Neurosurgery, St. Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea

Introduction: HFS of the subthalamic nucleus (STN) is recognized as an effective treatment of advanced Parkinson's disease. However, the neurochemical basis of its effects remains unknown. The aim of this study is to investigate the effects of STN HFS in intact and 6-hydroxydopamine (6-OHDA)-lesioned hemiparkinsonian rat model on changes of principal neurotransmitters, glutamate, and gamma-aminobutyric acid (GABA) in the striatum.

Methods: The authors examined extracellular glutamate and GABA change in the striatum on sham group, 6-OHDA group, and 6-OHDA plus DBS group using microdialysis methods. High-pressure liquid chromatography was used to quantify glutamate and GABA.

Results: HFS-STN induces a significant increase of extracellular glutamate and GABA in the striatum of 6-OHDA plus DBS group compared with sham and 6-OHDA group.

Conclusion: Therefore, the clinical results of STN-HFS are not restricted to the direct STN targets but involve widespread adaptive changes within the basal ganglia.

#101

WHERE, WHAT & HOW?

ADAPTATION OF CORTICO-SUBCORTICAL STIMULATION-TESTING TASKS TO CORTICAL PARCELLATION

Henry Colle (1), David Colle (1), Bonny Noens (1), Giovanni Alessi(1), Bob D'Haen (1), Erik Robert (2)

1. Neurosurgery, AZ St Lucas, Ghent, Belgium

2. Neurolinguistics, AZ St Lucas, Ghent, Belgium

Introduction: It seems obvious that cortico-subcortical mapping has to rely on more complex testing than object naming and counting.

The kind of testing depends on the stimulated area, on its anatomical and functional definition.

Till now, as well anatomical definition of the concerned area as the adapted application of testing are insufficiently accurate.

Cortical anatomical definition is provided by delimitation of gyri, but this division is too coarse for clinical practice.

Methods: For anatomical accuracy, the Cortical Parcellation System proposed by Corina (2010), however arbitrary, seems to be practical and internationally accepted

Unfortunately, the integration of the system in the preoperative planning is not yet available.

Results: We first present a method for application of the parcellation system on preoperative navigation planning.

The kind of testing is adapted to the presumed function of the cortical parcel, with phonological, semantic, syntactic linguistic tests, as well as non-linguistic cognitive testing.

Conclusion: The testing was applied on awake patients during cortico-subcortical mapping.

#126

Electrical stimulation of the medial forebrain bundle in pre-clinical studies of psychiatric disorders: a Review

Máté D Döbrössy (1), Luciano L Furlanetti (1), Volker A Coenen (1)

1. Dept. of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Freiburg, Germany

Introduction: Application of DBS has expanded from predominantly motor disorders into psychiatric disorders as well. Clinical trials of DBS in treatment resistant depression targets diverse brain regions associated with the pathology, with a study showing Medial Forebrain Bundle (MFB) stimulation producing rapid and stable anti-depressive effects. The MFB plays a key role in motor, reward orientated behaviors and affect regulation, and has now emerged as a promising stimulation target in psychiatric disorders.

Methods: The poster reviews the relevant pre-clinical literature identified using PubMed, examining the experimental outcome of electrical stimulation of regions associated with the MFB in the context of models of psychiatric disorders such as addictions, obsessive-compulsive disorder and depression.

Results: Pre-clinical studies of DBS in models of psychiatric diseases advance several legitimate stimulation targets, including the MFB. Mechanisms of action proposed include antidromic inhibition of corticostriatal pathways, or the enhancement of descending glutamatergic excitatory afferents to the VTA leading to its increased firing. However, the studies do not comprehensively explain how local stimulation impacts on global neurocircuitry or associated networks.

Conclusion: With promising but limited clinical data available, there is a need for improved understanding of the anatomy and the connectivity of the MFB and consequences of its stimulation in models of psychiatric disorders. Future experimental work will need to shed light on the anti-depressive mechanisms of MFB stimulation in order to optimize clinical interventions.

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High-frequency stimulation of the Medial Forebrain Bundle in rodents: Gender as a predictive factor influencing outcome

Inigo Aguirre (1), Luciano L Furlanetti (1), Máté D Döbrössy (1), Volker A Coenen (1)

1. Dept. of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Freiburg, Germany

Introduction: Recently, bilateral DBS of the medial forebrain bundle (MFB) has shown to relieve depressive symptoms in a clinical context. The mechanisms of this observation have been further investigated in experimental animal models. Although females are more vulnerable to develop clinical depression, most of the experimental studies have used male rats as models of depression. The aim of this study was to look at gender as a putative factor, affecting outcome after MFB stimulation.

Methods: Sprague-Dawley male/female adult rats (n=16) underwent bilateral stereotactic microelectrode placement into the MFB. Bilateral bipolar chronic continuous high-frequency stimulation (HFS) of the MFB was applied over three weeks in all the animals. Health supervision, behavior changes and post-mortem histological examination were performed. Immunohistochemical analysis to ensure correct electrode placement and to evaluate neurogenic changes, as well as to address c-fos expression induced by MFB-HFS was done.

Results: MFB-HFS produced a transitory loss of weight and also induced an increased seeking and searching behavior both in females and males rats. MFB-HFS showed to reduce anxiogenic-like behavior in females. Metabolic differences assessed by the measurement of corticosterone blood levels were not observed between groups. However glucose blood levels were altered after three weeks of stimulation. Following MFB-HFS, hippocampal neurogenesis in females was significantly decreased; upregulation of c-fos expression in the NAcc, limbic areas and LHb was also observed.

Conclusion: MFB-HFS is a reliable and safe instrument for further understanding of the mechanisms of electric neuromodulation of the mesolimbic pathways in the context of an experimental model of depression. MFB-HFS does not affect rat's welfare, but induces a transitory increase in motor activity and seeking behavior in both male and female rodents. Immunohistochemistry revealed stimulation-induced upregulation of c-fos expression in brain areas related to the reward system. Some gender differences were observed in post-stimulation behavior and histology, with female rats being responsive to HFS of the MFB.

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Simulated activation distances in a study of three different DBS-lead designs

Fabiola Alonso (1), Malcolm Latorre (1), Karin Wårdell (1)
1. Biomedical Engineering, Linköping University, Linköping, Sweden

Submitter: Melle Alonso Fabiola (SE)

Introduction: Deep brain stimulation (DBS) systems for Parkinson disease and other movement disorders have been dominated by one type of lead design for many years. New DBS leads are under development, in clinical evaluation, or already available. To increase the understanding of different lead designs, function and influence, a computer tissue model can be a useful tool set. The aim was to use modeling and simulation in order to compare the maximum activation distance for three DBS-lead designs.

Methods: The distribution of the electric potential in the vicinity of three DBS electrodes was simulated using 3D finite element method (FEM) models (COMSOL Multiphysics, COMSOL AB, Sweden). Models were set up for Lead 3389 (Medtronic Inc., USA), Lead 6148 (St Jude Medical Inc. USA) and Lead SureStim1 with 8 and 16 contacts (Sapiens Steering Brain Stimulations B.V., The Netherlands). The leads were surrounded by homogenous grey tissue ($\sigma = 0.09\text{S/m}$) and a peri-electrode-space ($250\mu\text{m}$) mimicking the chronic stimulation stage ($\sigma = 0.06\text{S/m}$). In all cases the second contact from the tip, C1 in lead 3389 or equivalent electrode position on the other leads was used. An axon cable model was constructed in MatLab. The influence of the respective cathodic monopolar DBS-stimulation for the excitation of nerve fibres ($D = 5\mu\text{m}$) passing perpendicular to the face of electrode were simulated ($n = 60$) for the pulse width $T = 60\mu\text{s}$, and the drive amplitudes VDBS (0.5 to 5V, steps of 0.5) and IDBS (0.5 to 5mA, steps of 0.5). The maximum activation distances from the surface of the respective leads were calculated and compared.

Results: There was a clear trend in all simulations, independent on lead design, of increasing distance for increased drive potential. A neuron activation distance of 3 mm was reached with VDBS range of 1.75 to 2.5V for all leads. For IDBS drive the 3 mm activation distance was reached with a drive range of 1.25 to 1.75mA. For a VDBS of 5V, the activation distance ranged from 4.25 to 5.02 mm, while in IDBS mode the 5 mA drive activation distance ranged from 5.0 to 5.6 mm. In voltage mode, the 3389 and 6148 Leads presented the same curve whereas the SureStim1-8 lead showed a parallel curve 0.4 mm shorter and SureStim1-16 reached 0.4mm further in distance. The contact area for the SureStim1-8 is 2.88 mm² for lead 3389, 5.98 mm² for lead 6148, 6.60 mm² and for the SureStim1-16 lead the contact area is 5.76 mm². With current drive mode, the leads all had parallel, but non overlapping curves with lead SureStim1-16 having the shortest distance at 3 mA drive of 3.9 mm, the SureStim1-8 having the furthest reach at 4.4 mm, and the other two leads located between these points.

Conclusion: The computer simulations indicate that the leads and configurations of the leads used in this study have similar outer extents for recruitment volume. The differences in activation distance between the leads is likely due to the differences in electrode surface area, as the simulated electrode material and intervening tissues were the same in all scenarios. Future studies will include a range of fiber parameters and pulse lengths for a broader understand of recruitment volumes in deep brain stimulation for different lead designs.

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The stereotaxic neurophysiology of the midbrain periaqueductal gray in the rat in vivo: An effective site for deep brain stimulation and autonomic control

Hari Subramanian (1), Terry Coyne (1), Peter Silburn (1)
1. UQCCR, The University of Queensland, Herston, Australia

Introduction: DBS has become an established neurosurgical treatment for Parkinson's disease, dystonia, and tremors. This is because neuroscientific research in mammalian animal models has contributed to improved understanding of brain circuitries underlying not only the pathology of PD, but also that bring about locomotor control and their inhibition/disinhibition. DBS is seen as an emerging technology for treatment of various psychiatric and neurogenic disorders, such as obsessive compulsive disorder (OCD) and autonomic disease. Autonomic diseases include breathing problems, hypertension and urinary incontinence and manifest either due to neurogenic dysfunction of brainstem autonomic control circuits and/or accompany psychiatric and emotional disorders. One 'stop shop' for treatment of autonomic disease could be DBS induced neuromodulation of the midbrain periaqueductal gray (PAG). The PAG is the critical real center of the limbic brain and maintains strong connections to the autonomic control circuits located in the caudal brainstem and spinal cord. Through these projections the PAG determines the level-setting of the whole body. This enables it to control not only neural circuits that generate and regulate breathing, blood pressure and bladder function, but also many motor components as vocalization, coughing, sneezing, vomiting, abdominal and intrathoracic pressure. Various types of autonomic deficits such as dyspnea, apnea, ataxic, asthmatic and sleep disordered breathing, hyper & hypotension and micturition disruption can be evoked by stimulating the PAG. However the PAG controls these not independently but integral to survival issues, such as emotional expression, coping strategies to pain, stress, fear and environmental danger. For example, strained breathing, i.e. contraction of laryngeal muscles with slowed breathing against airway resistance, seen in animals unable to escape danger or in humans experiencing stress and anxiety, can be evoked from the PAG. Thus DBS application in the PAG for treatment of isolated autonomic component should be assessed with caution. This is because multiple activations and/or spread of the stimulation effect (via DBS) could provoke a wide range of effects that cannot be easily controlled in the clinical setting. For this reason the neural architecture, circuit physiology/pharmacology and autonomic topography within the PAG needs to be investigated. Understanding of properties such as inhibition and disinhibition within the PAG, amplitude and temporal sensitivity of its neurons and chronaxie of its circuits would enable segregation of microcircuits that handle specific autonomic and motor components and consequently selective design and application of DBS. This would require fundamental investigation of the PAG neurophysiology in the animal model.

Methods: This investigation mapped the PAG stereotaxically for neuronal activity in the rat in vivo. Detailed electrophysiological characteristics such as burst frequency & adaptation, power & amplitude density, threshold activation constants, inter-spike intervals and the topography of neuronal circuit function was investigated.

Results: The PAG was found to be predominantly quiescent in the resting state. Silent PAG cells could be activated by iontophoresis of DL Homocysteic acid (DLH) an excitatory amino acid glutamate agonist. Cells made to fire in this manner ceased activity when either DLH ejection was terminated or by co-iontophoresis of muscimol (GABA agonist). Spontaneously active cells were very few, restricted to the dorsal PAG region and these cells recorded extracellularly typically fired in a slow and irregular pattern. Activation of either behavioural and/or autonomic interventions caused immediate activation of PAG neurons mainly in the lateral and ventrolateral PAG. In such instances, lateral and ventrolateral PAG cells showed two distinct types of activity patterns; 1) single spike firing and 2) burst firing. The cells fired both tonically and phasically when correlated with specific autonomic output such as the diaphragm EMG. Predominantly the non-bursting PAG neurons had a near normal distribution around 200 to 250 msec, while burst-firing cells typically showing a bimodal distribution.

Conclusion: The functional implications of PAG neuronal activity are thus discussed in terms of descending motor and autonomic control and effective translation for application of DBS in the treatment of autonomic disease.

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The role of 5-HT in depression in Parkinson's disease patients after deep brain stimulation of the subthalamic nucleus: evidence in subdural CSF?

M. Melse^{ac}, S.K.H. Tan^{ab}, A.F.G. Leentjens^d, Y. Temel^{ac}

^aDepartment of Neuroscience, Maastricht University, Maastricht, The Netherlands

^bDepartment of Neurosurgery, Universitätsklinikum RWTH Aachen, Aachen, Germany

^cDepartment of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands

^dDepartment of Psychiatry, Maastricht University Medical Center, Maastricht, The Netherlands

Introduction: DBS of the STN is an effective surgical therapy in the treatment of Parkinson's Disease (PD). Despite the beneficial effects on the cardinal PD motor symptoms, clinical experience and research have shown that STN DBS is accompanied by psychiatric side effects including depression, increased impulsivity and anxiety disorders in approximately 8% of STN DBS treated PD patients. The origin of the mood related side effects are unknown, but it is thought that the serotonin (5-hydroxytryptamine, 5-HT) neurotransmitter system plays a role. Recent animal research has indeed shown a strong link between STN DBS and a subsequent decrease in 5-HT release from the dorsal raphe nucleus, the brain's main serotonergic nucleus. An essential question is whether this also occurs in STN DBS treated PD patients. The aim is to determine the involvement of the 5-HT system in STN DBS induced mood related side effects in PD patients.

Methods: During STN DBS implantation procedures, we collect subdural cerebrospinal fluid (CSF) at two time points during the surgery. The first sample is drawn after incision of the dura before implantation of the first electrode (i.e. before intraoperative stimulation), and the second sample is drawn before implantation of the second electrode (i.e. after intraoperative stimulation). Non-PD patients receiving DBS electrodes serve as a control. Immediately after collection, the samples (~ 1ml) are put on ice, centrifuged and the supernatant is frozen. Samples are then analysed for 5-HT content by high performance liquid chromatography.

Results: We are still optimizing the analysis to determine whether 5-HT is detectable in the first place. So far, 4 control samples have been analysed. 5-HT levels seem detectable. We hypothesize that in PD patients 5-HT levels are significantly lower in the post-stimulatory sample compared to the pre-stimulatory samples and we expect no differences in non-PD patients.

Conclusion: We hope to finish the analysis of samples of 10 PD vs. 10 control cases by the beginning of next year.

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Deep brain stimulation influences the mesolimbic dopamine pathway.

M. Melse^{ab}, A. Jahanshahi^{ab}, S.K.H. Tan^{ac}, A.F.G. Leentjens^d, Y. Temel^{ab}

^aDepartment of Neuroscience, Maastricht University, Maastricht, The Netherlands

^bDepartment of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands

^cDepartment of Neurosurgery, Universitätsklinikum RWTH Aachen, Aachen, Germany

^dDepartment of Psychiatry, Maastricht University Medical Center, Maastricht, The Netherlands

Introduction: Parkinson's disease (PD) is a progressive neurological motor disorder generally attributed to a loss of dopaminergic transmission in the nigrostriatal dopamine pathway. High frequency stimulation (HFS) of the subthalamic nucleus (STN) improves motor disability in PD. However, approximately 8% of the PD patients receiving STN HFS experiences psychiatric side effects. These include depression, (hypo)mania and apathy. The origin of these mood related side effects are unknown. Generally, the serotonin neurotransmitter system is held responsible for mood changes. However, in view of its limbic involvement, the mesolimbic dopamine pathway can also be considered as a candidate mechanism leading to STN DBS induced mood changes. Originating in the ventral tegmental area (VTA), mesolimbic dopamine is transmitted to the ventral striatum, including the various subdivisions of the nucleus accumbens.

Objective: To investigate whether STN DBS induces changes in the mesolimbic dopamine transmission.

Methods: Naïve male Sprague Dawley rats were implanted with bilateral STN electrodes (HFS N=7 vs. sham N=7) and stimulated for 1 hour at clinically relevant parameters (130 Hz, 60 msec, 100 microA). After tissue processing, brains were stained immunohistochemically for c-Fos (activation marker) and tyrosine hydroxylase (dopaminergic marker) and a fluorescent double staining was performed. C-Fos activation in the VTA was assessed by semi-quantitative analysis and optical densitometry served to determine TH expression in the ventral striatum (nucleus accumbens core and shell and the medial tip of the shell) at 2 different bregma levels.

Results: HFS did not alter physiological behavior. STN HFS did not significantly change c-Fos expression VTA ($p>0.05$). However, in STN stimulated animals, TH expression levels in the ventral striatum (specifically the nucleus accumbens shell and medial tip of the shell) were significantly increased at the more caudal bregma level ($p<0.05$).

Conclusion: STN HFS at clinically relevant stimulation parameters significantly influences the mesolimbic dopamine pathway.