Epilepsy

Treatment of medically intractable partial seizures with responsive stimulation

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Introduction: The RNSÂ® System is an investigational cranially implanted responsive neurostimulator evaluated as an adjunctive therapy in individuals â‰¥ 18 years of age with medically refractory partial onset seizures from â‰¤ two foci.

Methods: 191 subjects across 32 centers were implanted and randomized 1:1 to active or sham responsive stimulation. Efficacy was assessed over a 12 week blinded period and a subsequent 84 week open label period (OLP; all subjects received stimulation).

Results: The average subject took 2.8 AEDs/day and had 1.2 seizures/day; 32% were previously treated with cortical resection and 34% with a VNS.

Seizures were significantly reduced from baseline during the blinded period in the active (-37.9%, N=97) compared to the sham group (-17.3%, N=94; p=0.012, GEE). In the OLP, the median % seizure reduction improved over time (44% at 1 year and 53% at 2 years, p<0.001). Verbal and visual-spatial function, memory, mood, and quality of life (QOL) significantly improved.

Adverse events (AEs) were not different between active and sham groups; rates did not increase over time. AEs affecting > 5% of subjects were EEG monitoring (7.3%) and increase in complex partial seizures (5.2%). Deaths were 4 SUDEP events, 1 suicide and 1 lymphoma.

Discussion: Responsive stimulation reduced seizures without increasing AEs compared to sham stimulation. The seizure reduction improved with time.

Conclusions: Treatment with the RNS System has the potential to reduce partial seizure frequency and improve QOL in persons with epilepsy intractable to medications and often to surgery and VNS, without mood or neuropsychological risks.

Epilepsy

Electrochemical Analysis of Dynamic Changes in Cortical Adenosine Correlate with Seizure Termination

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Introduction: Seizures are currently defined by their electrographic features. However, epileptic networks are intrinsically dependent on neurotransmitters but little is known about their peri-ictal dynamics. Evidence supports adenosine as having a prominent role in seizure termination, as its administration can terminate and reduce seizures in animal models. Further, microdialysis studies in humans suggest adenosine is elevated peri-ictally, but the relationship to the seizure is obscured by its temporal measurement limitations. Because electrochemical techniques can provide vastly superior temporal resolution, we test the hypothesis that adenosine rises during seizures in an animal model and humans using fast scan cyclic voltammetry (FSCV).

Methods: White farm swine (n=45) were used in an acute cortical model of epilepsy and 10 human epilepsy patients were studied during intraoperative electrocorticography (Ecog). Wireless Instantaneous Neurotransmitter Concentration Sensor (WINCS) based FSCV and amperometry were obtained utilizing an adenosine specific triangular waveform or biosensors respectively.

Results: Simultaneous Ecog and electrochemistry demonstrated adenosine rise at 7.5 Â± 16.9 seconds with amperometry (n=75 events) and 2.6 Â± 11.2 seconds with FSCV (n=15 events) prior to electrographic seizure termination. In agreement with this animal data, we also recorded adenosine elevation prior to seizure termination in a human patient utilizing FSCV.

Conclusions: Simultaneous Ecog and electrochemical recording supports the hypothesis that adenosine rises prior to seizure termination, suggesting that adenosine itself may be responsible for seizure termination. Future work using intraoperative WINCS based FSCV recording may help to elucidate the precise relationship between adenosine and seizure termination.

Epilepsy

Optogenetic Stimulation of the Medial Septum Controls Oscillatory Activity in the Hippocampus

Nealen Laxpati

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Introduction: Optogenetic stimulation of neural activity offers unparalleled control of neural networks. Control of hippocampal oscillations could prove a viable method of arresting or preventing epileptic seizures. Here we demonstrate that cell-type specific optogenetic activation of the medial septum (MS) is sufficient to generate corresponding oscillatory local field potential (LFP) activity in the dorsal hippocampus.

Methods: Sprague-Dawley rats were infected in the MS with AAV2-CaMKIIÎ±-ChR2, AAV5-hSyn-ChR2 or a control virus. After two weeks, each was anesthetized and implanted with an optical fiber targeting the MS and a 16-channel microwire multielectrode array (Tucker-Davis Technologies) separately and simultaneously targeting CA3 and CA1. Each animal underwent 473 nm blue laser stimulation at frequencies of 7, 11, 17, 23, 35, and 42 Hz and pulse widths of 1, 5, and 10 ms. Histology confirmed electrode, optical fiber, and infection locations, and recorded electrophysiological data was analyzed using custom-written Matlab scripts.

Results: Optogenetic control of cell-type specific neurons of the MS drove activity locally and in the dorsal hippocampus. An increase in stimulus frequency-specific power in the hippocampal LFP was observed during stimulation, but not in ChR2-negative controls. In addition, several hippocampal single units increased firing during stimulation.

Conclusion: We have developed a system for optogenetic stimulation and multielectrode recording, and used it to begin dissecting the neural circuitry of the septohippocampal system. Here we demonstrate support for the hypothesis that the medial septum serves as a pacemaker of hippocampal oscillations, and begin the task of identifying the specific cell types responsible for this activity.

Epilepsy

Evaluation of a Clinical System for Deep Brain Stimulation and Recording of Neural Network Activity

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Introduction: In conjunction with therapeutic stimulation, next generation DBS devices may offer advanced features, including the ability to record and analyze neural signals, providing unprecedented insight into DBS effects on neural networks, and the potential to titrate therapy based on physiological observations. The work reported here represents the first chronic evaluation of an implantable, clinical-grade system that permits concurrent stimulation and recording, using a large animal (ovine) model recently developed to study DBS for epilepsy.

Methods: Following anesthesia and 1.5T MRI acquisition, unilateral anterior thalamic and hippocampal leads were implanted in three animals using a frameless stereotactic system, and connected to modified neurostimulators. Chronic, awake recordings of evoked potentials (EPs) and local field potentials (LFPs) were collected with the implanted device and analyzed off-line.

Results: Hippocampal EPs to thalamic DBS were stable over extended periods of time (three cumulative â€œsubjectâ€ years of experience) and consistent in morphology and latency with prior acute results. Stimulation of thalamic and hippocampal leads produced both excitatory and inhibitory network effects that were target site and parameter dependent. Timed and event-triggered free-roaming recordings illustrated multiple activity patterns within this neural network (Papez circuit), including periods of highly correlated activity between the two structures.

Discussion & Conclusions: These results provide further insight into DBS therapy for epilepsy, and an encouraging demonstration of the capabilities of this new technology, which may afford unique opportunities to study human brain function and neuromodulation mechanism of action in ways that were previously unavailable.

Epilepsy

Implantation of Centromedian and Anterior Thalamic Nuclei for Epilepsy: Technical Discussion

Daniel Clayton

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Introduction

Both the centromedian and anterior nuclei of the thalamus have been targets for deep brain stimulation to control epilepsy, with a suggestion that each may be preferentially effective for different seizure types. Patients with multiple seizure types might benefit from implantation of electrodes at both target sites. Here we report on the technical issues related to bilateral dual target implantation.

Methods

7 patients with treatment refractory epilepsy were chosen to receive implants at both targets based upon their multiple seizure types. The target sites were identified using an MRI fused stereotactic atlas and comparison with published values. Non-intersecting trajectories were planned and standard frame-based stereotactic placement of all electrodes was performed with microelectrode recording. No adverse effects of stimulation were seen. The electrodes were connected to extension leads, and tunneled unilaterally to a 32 channel implantable stimulator.

Results

All 7 patients underwent successful implantation of 4 electrodes. Post-operative imaging confirmed accurate placement of all electrodes. All electrode contacts were tested, and although optimization of the stimulation parameters is still ongoing, stimulation of both targets on a side appears superior to either target on its own.

Discussion

The placement of electrodes into both the centromedian and anterior thalamic nuclei requires thoughtful planning of trajectories and careful management of the implanted cabling.

Conclusions

While the relative contribution of stimulation at each site is still to be determined, it can be concluded that bilateral targeting of both the centromedian and anterior thalamic nuclei can be performed safely and accurately.

Epilepsy

Interictal Spikes are associated with Inactivated Action Potentials in Epileptic Human Neocortex

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Introduction: Interictal spikes (IIS) and high-frequency oscillations (HFO) have been investigated in human epilepsy and are frequently associated with the ictal onset zone. The mechanisms of HFO generation and their potential role in the pathophysiology of epilepsy remain controversial.

Methods: Penetrating microelectrode arrays were implanted in the temporal or frontal cortices of nine patients undergoing invasive ECoG monitoring. Neuronal activity was recorded at 30 kHz. 4384 IIS were recorded and their high-frequency spectro-temporal dynamics and propagation were analyzed. Action potential firing patterns from 104 neurons were also analyzed. We performed in vitro simultaneous intracellular and extracellular recordings on six neurons in tissue resected from adjacent to a microelectrode array.

Results: Time-voltage plots of high-pass (>250 Hz) filtered electrophysiological data revealed bursts of high-frequency action potential-like activity during IIS. Averaged spectrograms exhibited increased power in the 250â€“600 Hz band during IIS. In vivo recordings showed that bursts of action potentials were synchronous with increased 250â€“600 Hz power and IIS. Intracellular recordings from neocortical slices and computational modeling showed that inactivated action potentials generated the increased 250â€“600 Hz power recorded during IIS.

Discussion: During IIS, the increased 250â€“600 Hz power arises from bursts of inactivated action potentials rather than oscillations in field potentials. Further, directional propagation of interictal spikes was consistently observed in the neocortex.

Conclusion: Propagation of IIS, and the associated bursts of inactivated action potentials, supports the hypothesis that IIS contribute to the progression of epilepsy by Hebbian recruitment of neurons into epileptic networks.

Epilepsy

Transmantle sign in cortical dysplasia: an excellent prognosis for seizure-control

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Introduction: Focal Cortical Dysplasia (FCD) represents a spectrum of developmental cortical abnormalities and is one of the most common causes of intractable epilepsy in children and young adults. In some FCDs, a transmantle sign can be observed on imaging to focally span the entire cerebral mantle from the ventricle to the cortical surface. Our aim was to characterize seizure control outcomes and prognostic significance of the transmantle sign (TMS) in FCD epilepsy.

Methods: We report 14 patients with TMS who underwent resective surgery for medically refractory epilepsy. Patient demographics, magnetic resonance imaging (MRI), electroencephalography (EEG), intraoperative electrocorticography (ECoG) and pathology were reviewed.

Results: All patients had childhood seizure onset, and concordant MRI and ECoG findings. The primary MRI findings associated with TMS include grey-white junction blurring, appearance of cortical thickening, T2 or FLAIR abnormality, and bottom-of-the-sulcus dysplasia. The TMS was usually a focal finding, usually confined to one or several gyri with well-circumscribed epileptic tissue. ECoG sensitivity detects abnormal tissue which sometimes extends beyond the MRI lesion. Correlation to FCD histopathological subtypes was variable and inconclusive. Patients who had complete resection of MRI and ECoG abnormalities (12/14 patients) became seizure-free.

Discussion: TMS is an under-recognized phenomenon within the spectrum of FCDs, with distinct radiographic and prognostic features. Our study highlights the favorable postsurgical outcome in patients with TMS. In our series, all patients who had complete resection achieved seizure-freedom, which is greater than other studies on FCD.

Conclusion: The transmantle sign is a unique feature seen in cortical dysplasias, and is particularly amenable to surgical treatment with highly favorable seizure control outcomes.

Movement disorders

Optogenetic Neuromodulation in the Primate Motor System

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Introduction: Electrical stimulation, while an essential clinical and research tool, has limitations. Optogenetics holds two advantages: (i) the control of genetically-specified populations of neurons in vivo while (ii) allowing simultaneous recording of neural activity. This approach holds promise for both primate neurophysiology and potential human therapies. We developed two primate optogenetic models, squirrel monkeys (Saimiri sciureus) and rhesus macaques (Macaca mulatta).

Methods and Results: In squirrel monkeys, using adeno-associated virus 2/5 (AAV5), we successfully transduced multiple opsins, both excitatory (channelrhodopsin-2, ChR2) and inhibitory (Natronomonas pharaonis halorhodopsin, eNpHR3.0) under pan-neuronal (human synapsin), and excitatory neuron specific (calmodulin-dependant kinase II, CamKIIÎ±) promoters. We developed an intraoperative single-unit recording system, allowing electrophysiologic opsin characterization. We noted both axonal transduction as well as distant transduction of neurons in both rhesus and squirrel monkeys, but not in rats, underlining the need for primate-specific optogenetic models. Squirrel monkeys provide valuable histologic data on opsin functionality.

Rhesus allow for complex behavioral study. We transduced excitatory and inhibitory opsins, including the red-shifted opsin C1V1 under the CamKII promoter in premotor cortex. During a delayed reaching task, perturbing neural activity during motor planning lengthened reaction times, demonstrating an effect similar to electrical microstimulation.

Discussion: Primate optogenetics will enable direct observation of neuromodulation, which may allow novel insights into multiple disease states, as well as potential human therapies.

Conclusion: These findings demonstrate the histological, electrophysiological, and behavioral efficacy of optogenetics and represent an expansion of tools for primate neuromodulation.

(Please note some of these data were presented at the Academy meeting.)

Movement disorders

A prospective pilot trial for pallidal Deep Brain Stimulation (DBS) in Huntingtonâ€™s disease (HD) â€“ p

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At present, there is no effective treatment or cure for HD patients. Therefore, based on the long-lasting successful treatment of other neurodegenerative movement disorders like Parkinsonâ€™s disease, DBS was evaluated. Questions remained concerning the optimal target.This phase I clinical trial is based on the hypothesis that DBS of the pallidum can reduce choreatic symptoms. In addition, it should demonstrate which part of the pallidum can be used effectively for specific features of HD. We report on 6 HD cases who underwent DBS of the pallidum (GPi/GPe region). 2 patients suffered from the Westphal variant of HD. Electrodes were stereotactically implanted under general anaesthesia, followed by the implantation of a generator system (Kinetraâ„¢, Medtronic). Patients were randomized to Gpi or GPe stimulation and cross over after 6 weeks. Best contact stimulation was applied for 3 months.
No perioperative complications occurred. The coordinates for the active contacts in the GPi/GPe range were adapted to individual anatomical changes. There were no differences in total UHDRS between GPi and GPe stimulation. However, not counted the 2 westphal patients, under DBS total UHDRS of the remaining 4 patients improved significantly (preop 46.7 to 35.5 at 6 mo postop, $p<0.01$). The most effective active contacts were in projection to the border of GPi (n=3) and GPe (n=3).
Systematic positive influence of DBS and its safety in HD patients is reported for the first time. In the context of the following MCT it will have to be clarified which patients group is the most suitable for DBS and which long-term results can be obtained.

Movement disorders

Transcranial MR guided focused ultrasound: is noninvasive neuromodulation possible ?

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Introduction: Advances in ultrasound transducer technology have enabled the precise delivery of acoustic energy through the intact human skull. MRI allows for stereotactic targeting, and MR thermometry provides continuous monitoring of the treatment intensity and location. Transcranial sonications can thus be performed for thermal ablation of deep brain targets in nonsedated patients.

Methods: An FDA-approved feasibility trial of unilateral Vim lesioning was conducted with tcMRgFUS in 15 patients with medication-refractory essential tremor. During serial titrations of acoustic power, the temperature and energy thresholds were recorded for tremor suppression and if other clinical symptoms developed.

Results: Overall tremor improved by 62% at three months following unilateral focused ultrasound thalamotomy. The treated, dominant limb subscores improved by 75% resulting in a substantial improvement in quality of life and disability measures. A temperature threshold for tremor relief or symptoms could be identified in each case. In four patients, transient intraprocedural symptoms, namely paresthesia, were reported and allowed for refinement of the final lesion placement.

Discussion: Confirmation of sensory thalamus is critical to accurately target Vim for the treatment of tremor. TcMRgFUS can precisely ablate deep brain targets. Preliminary results from this study suggests that noninvasive neuromodulation of sensory thalamus is feasible during low temperature sonications. Extensive brain mapping may be possible with nonthermal acoustic parameters which would aid in the verification of stereotactic targets and in the diagnostic identification of subcortical neuronal circuits.

Conclusion: Noninvasive brain mapping of sensory thalamus is feasible during focused ultrasound lesioning, and research continues with nonthermal ultrasound parameters.

Movement disorders

Emotional content of music modulates STN firing rates

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INTRODUCTION:
The devastating sequelae of Parkinsonâ€™s disease (PD) include motor, cognitive and emotional disruptions, but the neural substrates of nonmotor effects remain enigmatic. Previous evidence from local field potentials (LFP) suggest that the subthalamic nucleus (STN) is selectively suppressed by emotional pictures (e.g. Houeto 2005), but direct evidence for emotional modulation of STN neurons has been rare.

METHODS:
During the microelectrode mapping portion of STN-DBS placement, patients listened to 30s classical music clips, previously normed for emotional content (measured by valence; high/low = happy/sad, and arousal; high/low = exciting/calm). Offline, STN electrophysiological measures, including root mean square power (n=30) and single unit firing rate (n= 25), were analyzed.

RESULTS:
We found that both high and low valence music suppressed single-unit activity in the STN more than neutral pieces ($p = 0.01$). Similarly, high arousal music depressed activity more than low arousal ($p = 0.02$). Importantly, this modulation was found throughout the structure, including motor areas.

DISCUSSION:
These results demonstrate that single-unit firing in the STN is modulated by strong emotionality in music. The striking similarity of these results to earlier results from LFP responses to emotional pictures suggests that this effect is crossmodal, consistent with emotional deficits seen in PD. Future directions include expanding the emotional battery to include social stimuli, such as emotional voices.

CONCLUSION:
Single units throughout the STN showed firing-rate modulation to the emotional content of music, shedding new light on possible neural substrates mediating the enigmatic emotional side effects of PD and of STN-DBS therapy.

Movement disorders

Pediatric Deep Brain Stimulator Surgical Complications

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Introduction: Although deep brain stimulation (DBS) has become commonplace for treatment of adult movement disorders, little data is available about DBS treatment of childhood movement disorders. We present surgical complications in children 18 years and younger undergoing DBS placement in our institution.

Methods: We conducted a retrospective analysis of all children 18 years old and younger undergoing DBS surgery from September 2007 to September 2011 at Cook Childrenâ€™s Medical Center. All patients enrolled for DBS surgery undergo a rigorous consent process approved by our institutional review board in accordance with the current United States FDA Humanitarian Device Exemption status of this device for dystonia

Results: 53 surgeries to implant electrodes with awake microelectrode recording (105 lead placements) were performed. Four infections required removal of DBS hardware (7.5%), with 3 of the 4patients reimplanted successfully. Four patients (7.5%) suffered ischemia to the caudate nucleus during DBS implantation. 2 were asymptomatic and 2 had transient hemiparesis that resolved within one month. A seizure in a known epilepsy patient during electrode implantation necessitated intraoperative sedatives and phosphenytoin. Three patients required electrode revision due to poor treatment response attributed to suboptimal placement. Finally, fractures or disconnection of electrode wires entailed revision in three (5.7%) patients.

Conclusion: Pediatric DBS affords another viable treatment option that movement disorder teams can offer to these challenging patients. Although the overall complication rate for this group of children was 33%, most complications were transient or easily treated. This information enables families to learn about risks associated with DBS placement.

Movement disorders

DBS treatment of DYT1 Dystonia: a 10-year, 52 patient experience

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Introduction: Globus Pallidus Interna (GPi) deep brain stimulation (DBS) is an effective treatment for DYT1-associated dystonia; but long-term results are lacking. We describe the long-term effects of GPi-DBS in patients with DYT1 dystonia.

Methods: Retrospective chart review of 52 consecutive DYT1+ patients treated by a single surgical team (RA & MT) and followed for up to 120 months (mean: 39). Symptom severity was quantified with the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor (M) and disability (D) sub-scores.
Results: Relative to the baseline BFMDRS(M), average disease burden remaining after 24 months of stimulation (N=35, $P<0.01$) was 15%; 11% at 36 months (N=27, $P<0.01$), and 9% at 48 months (N=17, $P<0.01$). As assessed with the BFMDRS(D), disease burden was decreased to 23% at 24 months, 21% at 36 months, and to 24% at 48 months ($P<0.01$). Follow up of up to 10 years showed maintenance of decreased disease burden consistently below 20% for both motor and disability scores. Twenty-three (44%) of the 52 patients required no dystonia related medications at last follow-up. Infections requiring removal and later reimplantation of hardware occurred in 4/52 (8%) of the patients. Dystonic Crisis occurred in 3/52 (6%). Hardware malfunction including lead fractures occurred in 3/52 (6%) of the cases.

Discussion/Conclusion: GPi-DBS is an effective therapy for DYT1-associated torsion dystonia. Efficacy is maintained for up to 10 years. Neurologic complications are rare but long-term hardware related complications can be significant.

Movement disorders

Thalamic centromedian/parafascicular complex stimulation in medically refractory Touretteâ€™s syndrome

Wei Hu M.D. Ph.D.

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Introduction:
Deep brain stimulation (DBS) of the thalamus may be a therapeutic option in patients with Tourette syndrome (TS) refractory to pharmacological and psychotherapeutic treatment; however, it remains unclear which nuclear target is most effective in TS. We report the clinical outcome in five patients with TS who underwent DBS targeting the center of the centromedian/parafascicular complex (CM/Pf), 4 mm posterior to the previously described thalamic target at the anterior margin of CM/Pf.

Methods:
All five patients fulfilled DSM IV criteria for TS. Stimulating electrodes were implanted targeting the center of the thalamic CM-Pf, 5 mm lateral and 8 mm posterior to the mid-commisural point along the superior-inferior plane of the AC-PC line. Preoperatively, and again after optimization of DBS parameters each patients was tested with the Yale Global Tic Severity Scale (YGTSS).

Results:
The average reduction in the total YGTSS scores in the five patients was 62 percent (range 44 â€“ 80%). The tic severity sub scores improved by an average of 58 percent (range 38 â€“ 80%) while the impairment sub scores improved by an average of 64 percent (range 33-80%). Psychiatric comorbidities as assessed by the consulting psychiatrist were stable or improved in all cases.
Discussion:
These findings suggest that stimulation targeting the center of the thalamic CM/Pf reduces tic severity to a similar degree as that targeting the anterior CM/Pf. Further studies are needed to directly compare between these and other targets.

Conclusions:
Our study further supports the role of the CM-Pf DBS target in medically intractable TS.

Movement disorders

Clinical Study of Bilateral Pedunculopontine Nucleus DBS for Gait Freezing and Falling in PD

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Peter Silburn (none), Wesley Thevathasan (none)

Introduction: Pedunculopontine nucleus stimulation is an emerging therapy for gait freezing in Parkinsonâ€™s disease. However the precise effects of pedunculopontine nucleus stimulation on parkinsonian gait disturbance are unknown. The clinical application of pedunculopontine nucleus stimulation is controversial. For example, it is unknown whether bilateral stimulation is more effective than unilateral and whether caudal pedunculopontine nucleus stimulation (beneath the pontomesencephalic line) is effective. To address these issues, we assessed the impact of unilateral and bilateral caudal pedunculopontine nucleus stimulation on triggered gait freezing and on background deficits of unconstrained gait in Parkinsonâ€™s disease.

Methods: In a double blinded experimental study using spatiotemporal gait analysis, Parkinsonian patients with severe gait freezing implanted with caudal pedunculopontine nucleus stimulators were assessed during three counterbalanced conditions whilst â€˜off medicationâ€™; off stimulation, unilateral stimulation and bilateral stimulation. Results were compared to disease matched parkinsonian patients without gait freezing and healthy controls.

Results: Pedunculopontine nucleus stimulation improved objective measures of gait freezing, with bilateral stimulation more effective than unilateral. During unconstrained walking, Parkinsonian patients who experience gait freezing had reduced step length and increased step length variability compared to patients without gait freezing - however, these deficits were unchanged by pedunculopontine nucleus stimulation.

Discussion: Caudal pedunculopontine nucleus stimulation specifically improves gait freezing but not gait akinesia. This differs from dopaminergic medication and subthalamic nucleus stimulation which both improve gait akinesia. For optimal therapeutic effects, bilateral implantation should be considered.

Conclusions: Caudal pedunculopontine nucleus stimulation improves gait freezing with bilateral stimulation more effective than unilateral.

Movement disorders

Neuronal activity in the human subthalamic nucleus encodes decision conflict during action selection

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Introduction:
Optimal decision making relies on assigning value to competing alternatives and selection between those choices. Computational models suggest that action selection can be efficiently mediated by a central mechanism, the basal ganglia. The subthalamic nucleus (STN), which receives excitatory inputs from the cortex and has direct connections with the inhibitory pathways of the basal ganglia, is well positioned to play this role.

Methods:
We use microelectrode recordings captured during deep brain stimulation surgery as participants engage in a probability learning and decision task to demonstrate that the human STN plays an important role in action selection. We analyze single unit activity during the decision period, and correlate neural activity with decision conflict.

Results:
We demonstrate that spiking activity in the STN increases when participants are asked to make a decision, and that the level of spiking activity is modulated by the level of decision conflict. Specifically, trials involving high levels of decision conflict exhibit significantly higher firing rates than trials involving low levels of decision conflict.

Conclusions:
These data implicate a central structure, the human STN, as an important mediator of action selection during decision processes. This first direct measurement of human STN activity during a decision task is consistent with the computational and theoretical models role of the STN in action selection, and accord the STN an important position in mediating decision processes.

Movement disorders

Synchronization â€“ a new Independent Hallmark of Parkinsonâ€™s Disease

Zvi Israel

Aeyal Raz (none), Hagai Bergman (none), Reuben Shamir (none), Shay Moshel (none)

Introduction
It is widely believed that oscillations drive basal ganglia synchronization in Parkinsonâ€™s disease (PD). However, neuronal synchronization in PD has only been described as a marginal phenomenon, mainly related to tremor activity. This study aimed to define the relationship between oscillation and synchronization in the Parkinsonian STN.

Methods
The simultaneously recorded spiking activity from two parallel electrodes of 72 STN trajectories in 57 PD patients undergoing DBS surgery was analyzed.
Results
A total of 1,837 pairs of STN multi-unit sites were recorded. Calculating the average synchronization over the entire STN, no significant synchronization was found. Significant average synchronization was only found between sites in the dorsolateral oscillatory region (DLOR) while other sites remained unsynchronized. Furthermore, oscillation and synchronization were found to be independent phenomena.

Discussion
These findings help to recast the relationship between oscillations and synchronization in the Parkinsonian BG. Previous studies have shown significant spatial overlap between the DLOR and the STN sensorimotor area. The finding that the STN ventromedial non-oscillatory region (VMNR) (considered to be part of the limbic and associative BG network) remains unsynchronized is in line with the predominant motor nature of PD.

Conclusion
These results suggest that in addition to changes in discharge rate and pattern, synchronization inside the STN may be an independent pathophysiological hallmark of Parkinsonâ€™s disease.Synchronization might be utilized as a trigger for closed loop deep brain stimulation systems

Movement disorders

Is Two More Than One? Quantitative Comparison of Unilateral and Bilateral STN DBS for PD

Parag G. Patil

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Introduction: STN DBS is the established surgical treatment advanced Parkinsonâ€™s disease (PD). Recent research suggests that bilateral stimulation can result in worse dual task cognitive-motor performance when compared with unilateral stimulation. The goal of this study was to perform quantitative cognitive-motor assessments during unilateral and bilateral DBS.

Methods: We studied 18 PD patients with bilateral STN DBS while off medication under conditions of bilateral stimulation (BStim) and unilateral stimulation (UniStim) to each side. Grasp force timing was assessed by utilizing a continual sine wave tracking grasp/ release task. The force tracking was performed under single and dual task conditions using a spatial and verbal working memory task as a secondary cognitive load.

Results: Temporal force tracking was significantly degraded on the left hand during all stimulation conditions. Ipsilateral UniStim resulted in poorer performance on the right hand with dual verbal working memory loads, whereas improved performance was seen under BStim and ipsilateral UniStim on the left hand with spatial memory loading.

Discussion: These findings suggest that temporal grasp control is better with BStim; however UniStim may be differentially as effective for grasp control depending on the side of stimulation and the type of cognitive working memory load.

Conclusions: Unilateral and bilateral stimulation may have significantly different effects among patients with PD treated with STN DBS.

Neuro-imaging

Accuracy of Interventional MRI-Guided DBS Implantation Using a Novel Stereotactic System: Initial C

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Introduction: Interventional MRI guided DBS implantation is an alternative to traditional frame-based surgery and uses anatomic targeting with real-time imaging instead of physiological localization. A commercially available system (ClearPoint), optimized for these procedures, is now available.

Methods: Prospective analysis of 48 consecutive implantations using ClearPoint in a Philips 1.5T MRI. Radial error (vector difference between intended and actual placement) was determined on the MR slice used for intraoperative target selection (STN = 4mm below AC-PC, GPi = at AC-PC).

Results: 48 electrodes were placed in 25 patients; 33 STN (31 Parkinsonâ€™s, 2 dystonia) and 15 GPi (5 Parkinsonâ€™s, 10 dystonia). The mean radial error was 0.6mm (SD=0.4mm), and was not statistically different for the two targets (p=0.34). 96% (46/48) of electrodes were placed with one pass, with none requiring more than two. There was one IPG infection requiring explantation, one symptomatic hemorrhage and one case with diplopia.

Discussion: The mean radial error of 0.6mm with ClearPoint was significantly less than the 1.0mm (SD=0.6mm) radial error obtained with 82 implants in a previous skull mounted aiming system (Medtronic Nexframe, two sample t-test $p<0.001$). The vast majority of electrodes were place in one pass, suggesting that the targeting accuracy of the system is consistent. The only infection in the series occurred at the IPG site and was not attributed to the iMRI procedure.

Conclusions: iMRI DBS implantation with the ClearPoint system resulted in sub-millimetric accuracy and a low complication rate. Technical pearls for optimal use of the system will be discussed

Neuro-imaging

Diffusion tensor imaging to aid subgenual cingulum target selection for DBS in depression

Dr Kartik Dev Bhatia

Dr Kartik Bhatia (none), Dr Luke Henderson (none), Professor George Ramsey-Stewart (none), Professor James May (none)

Introduction:
The most investigated target for deep brain stimulation (DBS) in depression is the subgenual cingulate gyrus (Cg25) which has been shown to be a critical hub for signalling in the condition. Diffusion tensor imaging (DTI) may be useful in locating the area of maximal tract crossover adjacent to Cg25 so as to best modulate the underlying circuits. We aimed to determine if there was a significant difference in the three-dimensional location of targets selected using DTI compared with standard T2 sequences.

Methods:
59 non-depressed adult volunteers underwent MR imaging using T2 and DTI sequences of the brain. Each patient had targets selected for both hemispheres using both T2 and DTI sequences.

Results:
There was a significant difference in the medio-lateral (x) and dorso-ventral (z) coordinates of DTI targets when compared with T2 targets ($p<0.001$). In addition, tracts linking Cg25 to the orbitofrontal cortex, nucleus accumbens, amygdala, and hypothalamus were consistently identifiable using DTI sequences.

Discussion:
There is significant inter-individual variability in the exact location of the white matter tracts that underlie Cg25. This study demonstrates that the area of maximal tract crossover can be identified and selected as a target using DTI. Such targets would allow treatment teams to modulate a greater number of structures in the circuits that underlie depression through a single site.

Conclusions:
Targets within Cg25 selected using DTI are significantly different in location to those using T2 sequences and can be consistently reproduced to identify the area of maximal tract crossover.

Neuro-imaging

Stereotaxy with Real-time MRI-Guided Robot Assistance

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Introduction: Stereotaxy involves hundreds of steps to be performed with millimetric precision. Precision becomes increasingly important when delivering biologic substrates to exact locations at predetermined rates. Real-time feedback using MR imaging allows for such delivery; robotic assistance improves ergonomics inside the scanner bore. We have developed an MRI-compatible prototype robotic system for automated targeting, alignment and delivery.

Methods: It consists of a robotic cannula guide residing in the scanner, MRI robot controller that resides beside the bed and navigation workstation in the console room. The robot is constructed of high-strength plastic, actuated by piezoelectric motors, and is kinematically similar to stereotactic head frames. Cannula placement was performed in 3T MRI selecting targets in sheep brain using Slicer navigation software. MRI compatibility was evaluated using four standard imaging protocols.

Results: Compatibility tests demonstrated no statistically significant degradation in image quality ($p<0.05$) with the robot in motion during imaging. Accuracy tests demonstrated robot motion can be controlled to 0.03mm. Initial trials in ex vivo sheep brain demonstrate full system integration.

Discussion: The experiments demonstrate feasibility including planning, visualization, tracking and robot motion. The robot is ergonomic and able to operate as live MR images are acquired without deteriorating image quality.

Conclusion: Synchronous automation and real-time MRI feedback may allow for the efficiency to overcome the obstacles which have impeded MRI-based procedures and robotics in neurosurgery. Benefits are most significant in cases where more than one trajectory is needed and frame adjustment required.

Neuro-imaging

In-Vivo Segmentation of the Human Amygdala using Diffusion Tensor Imaging and Probabilistic Tractogr

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Introduction: The purpose of this study was to use probabilistic tractography to functionally segment the amygdala and analyze its connectivity to other brain structures in vivo.

Methods: MRI brain sequences were obtained for a series of 7 healthy volunteers. 20-direction DTI was acquired. Seed masks for the amygdala were generated using FreeSurfer and probabilistic tractography was performed using FSL. The probability of connection between the amygdala and the rest of the brain was determined. The resulting connectivity matrix was subjected to k-means clustering for 3 groups. The resulting amygdala subgroups were analyzed for their connectivity to various cortical and subcortical regions.

Results: Amygdala segmentation yielded 3 consistent subgroups: superomedial, inferomedial and basolateral. The basolateral group showed greatest connectivity to the temporal lobe, insula, brainstem and cerebellum. The basomedial group showed greatest connectivity to the frontal, lateral prefrontal, and cingulate gyri. The superomedial group had greatest connectivity to primary motor cortex and orbitofrontal cortex. All 3 subgroups projected similarly to the hippocampus and striatum.

Discussion: Animal studies have shown a potential role for DBS of the amygdala in the treatment of conditions such as PTSD, depression and epilepsy. Based on differences in connectivity, subnuclei within the amygdala are likely to play separate functional, pathologic and therapeutic roles.

Conclusion: DTI-based probabilistic tractography can be used to derive an in-vivo patient-specific connectivity map of the human amygdala. This map may be used in the future for pre-operative planning and refinement of DBS targeting within the amygdala to functionally relevant subregions.

Neuro-imaging

Definition of a Stereotactic 3D Model of the Human Insula for Neurosurgical Approach (Epilepsy and S

Afif AFIF

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Objectives
Design a method for 3D reconstruction of the insula, including its gyri and sulci , in AC-PC reference usable individually for imaging or for epilepsy and stereotactic surgery.
Materials â€“ Methods

Morphometric study using 100 MRI of normal insular region. 56 male/44 female, 50 left/50 right hemispheres.

Stage 1 : Reconstruction in AC-PC reference of the insula from 3D-T1-MRI slices 1 mm thick.
Stage 2 : Digitalization and superposition of data in 3D using PhotoStudio software (Photo Editing Software) system with PC as the center of coordinates.

Stage 3 : MATLAB software (Mathworks Inc.) was used to transform in color values each pixel to obtain a color scale corresponding to the probability of insula sulci localization between 0% and 100%.

Results
Demonstration of very significant correlations between the coordinates of the main insular structures (angles, sulci ..) and the length of AC-PC.

This close correlation allows to describe a method for 3D reconstruction of the insula on MRI slices that requires only the positions of Ac and PC and then the inter-commissural (AC-PC) length. This procedure defines an area containing insula with 100% probability.
Conclusion
3D reconstruction of insula will be potentially useful for:

1- To improve localization of cortical areas, allowing to differentiate insular cortex from opercular cortex during stereoelectroencephalographic exploration of patients with epilepsy (SEEG) or in morphological and functional imaging.

2 - For microsurgical approach of Insula using Neuronavigation techniques.

3 - Identification of Insula during stereotactic surgery (SEEG, biopsy).

Keywords: Insul , 3D MRI, cerebral, Epilepsy.

Neuro-imaging

Magnetic Resonance Image Distortion Of Leksell Stereotactic Frames

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Introduction: Accurate and precise localization of intracranial targets is the foundation of image-guided functional neurosurgery, however, accuracy can be limited by image distortion. In this study, we tested whether magnetic resonance imaging (MRI) distorts the central fiducial location on Leksell stereotactic frames and whether this distortion is related to frequency encoding direction or affected by sinuses.

Methods: Ten patients undergoing pre-operative stereotactic 1.5T MRI for functional neurosurgical procedures were imaged with a T1 Spoiled Gradient Echo sequence and a repeat sequence with reversed frequency encoding direction. Stereotactic fiducial coordinates were obtained from equivalent slices in each patient. Distortion was quantified using the distance formula to calculate the distance of the central fiducial from the line produced by the flanking fiducials on the Leksell frame.

Results: Image distortion caused a significant shift in the central fiducial away from the line between the flanking fiducials (Avg: 1.01 mm, SD: 0.35 mm; $p < 0.01$). The frequency encoding direction determined shift direction. Sinuses containing air did not affect the magnitude of fiducial shift.

Discussion: These results demonstrate that MRI distorts fiducial location in Leksell frames, which can decrease stereotactic accuracy. Magnetic susceptibility artifact of the fiducial causes the distortion. This study emphasizes how MRI sequence and frame design influence surgical accuracy, which should be considered during surgical planning and as new stereotactic systems are designed and implemented.

Conclusions: Distortion from MRI shifts the central fiducial of Leksell stereotactic frames, which should be taken into account during surgical planning for functional neurosurgical cases.

Neuro-imaging

Decoding single trial visual processing dynamics from temporal cortex

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Introduction: Inferior temporal brain areas are known to have sub-regions that are specialized for processing specific categories of stimuli, and the â€œfusiform face areaâ€ is the most well known of these. These areas have primarily been identified in fMRI, and, at the ~5s timescales fMRI averages over, the single-trial dynamics of category-specific processing are unknown.

Methods: Sub-dural electrocorticographic (ECoG) electrodes were placed on the inferior temporal brain surface for of 6 human subjects, for seizure monitoring. Simple pictures of faces and houses (with blank screen in between) were shown for 400ms at a time. A real-time correlate of local neural population activity (so-called â€œbroadband spectral changeâ€) was extracted from the ECoG signal, using a singular value decomposition of the voltage power spectrum.

Results: Broadband change reveals a robust spatial relationship between face (lateral) and house (medial) picture selective sites. The timing (to within 20ms) and type of visual stimulus can accurately be predicted on single trials. The time to peak activity is faster and the total amount of processing is greater for novel stimuli (e.g. faces following houses and vice-versa), than it is for repeated within-class stimuli.

Discussion: Our results suggest that the timing and content of visual stimuli can be decoded in realtime. Furthermore, the brain adapts the speed and amount of processing for specific categories of objects observed in the world on a sub-second timescale, such as those that might be seen scanning through a landscape.

Neuro-oncology

Cortical stimulation induces topographic plasticity to enhance resection of tumors in Broca's area

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Introduction. The presence of functional areas within gliomas prevents their complete resection. It has been recently demonstrated that slow tumor invasion promotes topographic plasticity allowing staged tumor resection. We aimed to produce a â€œvirtual lesionâ€ in eloquent areas located within tumors either using repetitive transcranial magnetic stimulation (rTMS) or continuous high-frequency cortical electrical stimulation (HFCS), in order to promote plasticity and increase the extent of tumor resection. Methods. In 3 cases of gliomas invading Broca's area (1 astrocytoma, 1 oligodendroglioma, 1 anaplastic astrocytoma), previously partially removed using awake cortical monitoring, we stimulated with either rTMS (1 patient), or HFCS through an implanted subdural grid (2 patients), over the eloquent cortex located within the tumor remnant, associated to intensive logopedy. Stimulus intensity was set daily to the threshold of mild speech disturbance.

Results. While rTMS produced a reinforcement of fluent speech tasks, but not topographic plasticity, HFCS achieved the displacement of speech functions, and a more radical resection was possible in a repeated surgery. Reorganization of motor language areas was demonstrated with functional magnetic resonance and cortical stimulation. Motor language areas were identified at the right hemisphere where previously they were absent, or at different places at the left hemisphere than previously found.

Discussion. We provide the first evidence of induced topographic plasticity using HFCS in eloquent areas within a tumor, allowing an increased tumor removal. These results have important implications in brain tumor surgery, rehabilitation and reparative neuroscience.

Conclusions. Continuous HFCS induces topographic plasticity and allows enhanced tumor resections.

Neuro-oncology

The role of fMRI and DTI incorporated in neuronavigation system & CS in eloquent cortex lesions

Amandeep Kumar

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Aims & Objectives
To effectively use the three modalities viz functional MRI(fMRI), diffusion tensor tractography(DTI) and cortical stimulation(CS) in combination to localize the eloquent cortex and to effectively prevent the development of neurological deficits in surgery for eloquent cortex lesions.

Matreial & Methods
Fifteen patients with eloquent cortex lesions were included in our study. Preoperative fMRI and DTI were performed in all patients and then integrated into the neuronavigation system. Intraoperative cortical stimulation of sensorimotor cortex was performed to localize the eloquent cortex while the patients underwent awake craniotomy and comparison between cortical stimulation-tested areas and fMR imagingâ€“activated foci was made on the exposed cortical surface. Similarly, subcortical stimulation was compared with the tracts localized with DTI. Development of fresh neurological deficits after surgery was noted.

Results
A total of 127 cortical sites were evaluated with cortical stimulation in 15 patients. The overall sensitivity, specificity and accuracy of fMRI were 79%, 85% and 82% respectively. The risk of developing persistent neurological deficits was 6%.

Conclusions
Simultaneous integration of fMRI, DTI and CS under awake conditions increases the accuracy of localization of motor cortex. The study demonstrated that fMRI images do not always correspond to areas identified with CS, hence performing these procedures under general anaesthesia may precipitate neurological deficits.

Neuro-oncology

Single-fraction Radiosurgery of Benign Intracranial Meningiomas

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Introduction: Stereotactic radiosurgery (SRS) of benign intracranial meningiomas is an accepted management option. This study was performed to determine factors associated with tumor control and neurologic complications after single-fraction SRS.

Methods: Retrospective review of 416 patients (304 women/112 men) having single-fraction SRS for imaging defined (n=252) or confirmed WHO Grade I (n=164) meningiomas from 1990-2008. Excluded were patients with radiation-induced tumors, multiple meningiomas, Neurofibromatosis type 2, and prior or concurrent radiotherapy. The median tumor margin dose was 16 Gy (range, 12-20). The median follow-up was 60 months (range, 6-234).

Results: The 5-year and 10-year local tumor control (LC) rate was 96% and 89%, respectively. Male gender (HR=2.5, P=0.03), prior surgery (HR=6.9, P=0.002) and patients with tumors located in the parasagittal/falx/convexity regions (HR=2.8, P=0.02) were negative risk factors for LC. Forty-five patients (11%) developed permanent radiation-related complications at a median of 9 months after SRS. The 1-year and 5-year radiation-related complication (RRC) rate was 6% and 11%, respectively. Risk factors for permanent RRC were increasing tumor volume (HR=1.05, P=0.008) and patients with tumors of the parasagittal/falx/convexity regions (HR=3.0, P=0.005).

Discussion: Single-fraction SRS at the studied dose range provided a high rate of tumor control for patients with benign intracranial meningiomas. However, because only 34 patients (8%) had radiation doses below 14 Gy, the LC rate for low-dose benign meningioma SRS could not be analyzed.

Conclusions: Patients with small-volume, non-operated skull-base or tentorial meningiomas had the best outcomes after single-fraction SRS.

Neuro-oncology

Utility of OsiriX v.3.9.4 for intracranial tumor volume estimation in Laser-Induced Thermal Therapy

Nitesh V Patel

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Introduction
MR-guided Laser Interstitial Thermal Therapy (LITT) is used for treating intracranial tumors. Associated changes have not been quantitated and current methods for volume estimation maybe inaccurate. This study seeks to: 1) Analyze lesion size pre/post LITT; 2) Compare OsiriX (v3.9) and linear measurement-based volume determination methods.

Methods
The Visualase Thermal Therapy System (Visualase, Inc, Houston, Tx) was used. Two raters examined MR images of 12 subjects with varying intracranial neoplasms at the following time-points: pre-ablation (PreA), immediate post-ablation (IPA), and 24 hours post-ablation (24PA). Three assessments were involved: A) Tumor volumes and ratios for time-points using OsiriX to quantify size change. B) Linear-measurements from three planes were used to estimate PreA volumes. The two volume methods were compared. C) Paired two-tailed t-tests and correlation analysis were used to assess inter-rater reliability.

Results
Ablation ratios ranged 60%-473% (mean=187%). Volume changes were: mean IPA/PreA of 240% (st. dev. 131%), mean 24PA/PreA of 158% (st. dev. 91%), and mean IPA/24PA of 162% (st. dev. 66%). IPA volumes exceeded both PreA and 24PA volumes ($p=0.0003$ and $p=0.008$, respectively); however, 24PA and PreA volumes were similar. Linear-measurement volumes were, on average, 8.96 times larger than OsiriX volumes ($p=<0.004$). Despite no significant differences between raters, there was stronger correlation for OsiriX Volumes ($r=0.96$, $p=0.003$) than for linear-measurement volumes ($r=0.38$, $p=0.21$).

Conclusions
Although IPA volumes are larger than the PreA volumes, at 24 hrs there is a return to PreA size. Further, OsiriX has greater inter-rater reliability than linear measurements for lesion volume determination.

Neuro-oncology

GAMMA KNIFE RADIOSURGERY FOR TRIGEMINAL NEURALGIA: A DOSE COMPARISON

Warren Boling

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Introduction: The optimum dose of Gamma Knife Radiosurgery (GKR) for intractable TN has not been determined.

Methods: This retrospective analysis evaluated patients treated with GKR at West Virginia University, 2002-2009. All patients were contacted for follow-up interviews. Treatment was a single shot 4mm collimator centered on the proximal nerve. The early maximum dose was 80Gy. In 2005 the protocol changed to 85Gy. This study evaluates two radiosurgery doses for efficacy, side effects, and patient satisfaction.

A Kaplan-Meier statistic (K-M) analyzed duration of pain freedom. Log-Rank test compared the two dose groups. Chi-squared test compared categorical data.

Results: Sixty-Eight TN patients were treated. Three patients with MS and 2 with no post-treatment follow-up were excluded. Typical TN was treated with 80Gy in 27 patients, and 85Gy in 38. Mean age was 71 years. Twenty-seven were women. Fifteen had a prior procedure for TN (10 in 80Gy group, P=0.6). Mean follow-up post-GKR in pain-free patients was 44 months (range 6 to 114) treated with 80Gy and 34 months (range 6 to 80) treated with 85Gy. Four reported a sensory disturbance after 80Gy (16%) and 10 after 85Gy (27%) (p=0.4). One was bothered by numbness in the 80Gy group and 2 were annoyed in the 85Gy group. K-M analysis showed at 29 months 50% patients failed after 80Gy, and 79% had continued pain relief after 85Gy (P=0.03).

Conclusion: 85Gy for TN may provide a more robust pain relief compared to 80Gy with a trend to more sensory changes at a higher treatment dose.

Neuroprosthesis

Intracortical Brain-Computer Interfaces: The BrainGate Pilot Clinical Trials

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Introduction: Intracortically-based brain-computer interfaces hold the potential to restore communication, mobility, and independence for people with paralysis. The ongoing pilot clinical trials of the BrainGate Neural Interface System (IDE) are providing valuable clinical experience in chronic neuronal ensemble recording and in the development of intracortically-based assistive devices.

Methods: Seven people with tetraplegia from spinal cord injury (2), brainstem stroke (2), or ALS (3) have participated to date. A 4x4mm array of 96 microelectrodes is placed into the precentral gyrus; action potentials, multi-unit activity, and local field potentials are recorded simultaneously from each electrode. Signals transmitted via percutaneous connector provide for real-time decoding and external device control directed by the intended movement of the participantâ€™s arm or hand.

Results: Progress has been made toward the BrainGate-based control of communication devices by people with locked-in syndrome, as well as multi-dimensional control of prosthetic/robotic limbs and simulated functional electrical stimulation devices by people with tetraplegia. One participant used the device for more than five years. Challenges have been identified related to signal nonstationarities, surgical technique, and implanted device engineering. There have been no unanticipated adverse device effects.

Discussion: The BrainGate trials provide an unprecedented opportunity to develop and test a novel, potentially powerful restorative neurotechnology for people with paralysis. Fully implanted systems and several critical translational neuroscience concepts are the focus of ongoing research and development.

Conclusion: The BrainGate trials are providing novel neurologic, neurosurgical, neurorehabilitation, and neuroengineering insights, and have provided the basis for expanded related research.

Neuroprosthesis

Decoding Arm Kinematics from ECoG Signals in Humans During a Reach Task

Chandan Reddy

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Introduction:
Recent work has demonstrated the feasibility of long term decoding of arm kinematics using ECoG signals in monkeys.

Methods:
Following subdural grid implantation for mapping of epileptic foci, our subject was asked to perform a series of right arm center-out reach tasks. Limb trajectory was tracked with motion sensors that were placed on the shoulder, elbow, wrist, and distal interphalangeal joints. Subdural field potential (ECoG) signals were recorded simultaneously from the contralateral hemisphere. Using partial least squares (PLS) regression, a PLS decoder was built using 25% of the data to estimate weights for each of the 6400 features and validated on the remaining 75%.

Results and Discussion:
Our ECoG-based algorithm incorporated spectro-temporal features from multichannel ECoG data across multiple cortical areas and permitted 3D limb trajectory to be accurately decoded. After feature shuffling, the correlation between observed and predicted kinematics decreased to near zero. When given a novel brain signal from the remaining four blocks, the 4-component based algorithm of the first block successfully predicted sensor position with comparable accuracy, proving its robustness from one block to another (cross-block prediction). Accuracy was comparable to predictions published using ECoG signals and SUA in monkeys. Correlation Values (r) of the cross-block predictions did not differ significantly from same-block predictions ($p=0.3$) indicating that accuracies between same-block and cross-block predictions were similar.

Conclusion:
Multi-joint 3D positions were successfully decoded during a reach task in humans. With two minutes of training data, we successfully generated a stable algorithm over four seven-minute blocks.

Neuroprosthesis

Phase-amplitude coupling in the human hippocampus predicts successful memory encoding

Bradley Lega

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Introduction: Phase-amplitude coupling (PAC) has been observed in rodents during the encoding of episodic memories. Its role in human memory encoding has not been established. Specifically, we sought to identify a link between slow-theta (2.5-5 Hz) oscillations and gamma oscillations during memory encoding.

Methods: We analyzed our database of intracranial electrodes (278 electrodes in 46 patients) using Morlet wavelet decomposition to identify PAC in the hippocampus as participants engaged in the Free Recall task, a standard test of episodic memory. We looked for differences in PAC between successful and unsuccessful memory encoding.
Results: PAC in the hippocampus is most prominent between the phase of slow-theta (2.5-5 Hz) oscillations and the amplitude of high gamma (70-200 Hz) oscillations (theta-gamma cross-frequency coupling). The magnitude of PAC is significantly greater during successful encoding, consistent with animal data.

Discussion: PAC appears to be a method of organizing information in the human hippocampus during memory. Examining the preferred phase of coupling between slow theta and gamma oscillations during both encoding and retrieval may further characterize this relationship. The importance of slow-theta oscillations in human episodic memory is consistent with our published data showing increases in amplitude during successful encoding.

Conclusion: Using spectral analytic methods, identification of brain sites that are important for memory formation, including PAC, is possible. This can perhaps serve as the basis for a neuroprosthetic device for enhancing memory formation.

Pain therapies

Deep Brain Stimulation of the Nucleus Accumbens for Central Post-Stroke Pain

Grant Mallory
(University Grants/Research Support, Company: This work was supported by NIH (K08 NS 52232 award to KHL)), (University Grants/Research Support, Company: Mayo Foundation (Research Early Career Development Award for Clinician Scientists award to KHL)), (Fiduciary Position [of any organization outside the AANS], Company: Dr. Stead serves on the Medtronic Medical Advisory Board), (Fiduciary Position [of any organization outside the AANS], Company: Dr. Watson consults on the safety monitoring committee for Nevro CorpÂ® spinal cord stimulators)

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Introduction: Although effective for some chronic pain syndromes, deep brain stimulation (DBS) for central post-stroke pain (CPSP) has had limited success. The most commonly chosen pain targets are the periventricular gray (PVG) and ventralis caudalis of the thalamus (VC). Despite limited success in CPSP, few alternative targets have been explored. Here, we report results of combined stimulation using the nucleus accumbens (NAC), a limbic structure within the ventral striatum involved in reward and pain processing.

Methods: Two patients underwent DBS surgery for CPSP with implantation of the NAC, VC, and PVG and trial stimulation. Pain ratings were followed using a visual analog scale (VAS).

Results: Trial stimulation revealed decreased VAS scores by 80% with NAC and PVG stimulation. These electrodes were connected to a pulse generator and permanently implanted. Patients were followed 8 and 12 months respectively. At 3 months, both reported continued pain relief. Individual stimulation of each was tried at further follow up intervals. Neither received a durable response from individual stimulation, though reported benefit with combined stimulation.

Discussion: We report durable response with combined stimulation of NAC and PVG for CPSP, a combination previously untried. NAC stimulation may be an effective pain target, though reproducibility will need to be confirmed in randomized controlled trials, and the analgesic mechanisms will need further exploration.

Conclusion: Further investigation of DBS of the NAC should be conducted for CPSP.

Pain therapies

Transcranial magnetic resonance-guided focused ultrasound and the non-invasive central lateral thala

Daniel Jeanmonod
(Industry Grant Support, Company: InSightec Ltd (Haifa, Israel))

Transcranial magnetic resonance-guided focused ultrasound and the non-invasive central lateral thalamotomy against neuropathic pain: clinical, neurophysiological and targeting accuracy data

D. Jeanmonod, D. Moser, A. Magara, M. Kowalski

Introduction
Recent technological developments have opened the field of therapeutic application of transcranial MR-guided focused ultrasound (TcMRgFUS) to the brain through the intact cranium. The goal of this study was to get further clinical and quantitative EEG experience in the treatment of chronic, severe and therapy-resistant neuropathic pain with this technology, as well as to confirm its targeting accuracy.

Methods
In 12 patients, FUS thermocoagulations were performed uni- or bilaterally in the posterior part of the central lateral thalamic nucleus at peak temperatures between 51Â° and 58Â° with the help of real-time MR thermometry guidance.

Results
At 3-month follow-up, 9 patients had a mean pain relief of 55.6%, a mean improvement of their visual analogue scale ratings of 39.8%, and a reduction of their quantitative EEG spectral overactivities was observed particularly in the delta and theta frequency bands. The mean absolute targeting accuracy for 16 targets was 0.34 mm for the mediolateral dimension, 0.4 mm for the anteroposterior dimension and 0.68 mm for the dorsoventral dimension. There were no complications.

Discussion
This study expands and confirms the already published evidence on TcMRgFUS in the treatment of neuropathic pain. This technique avoids all surgical risks related to brain penetration, and the real-time continuous MR-thermometry allows an optimized lesioning safety and accuracy.

Conclusion
TcMRgFUS offers a safe, precise and efficient approach in the treatment of neuropathic pain.

Pain therapies

Percutaneous destructive procedures for intractable cancer pain: technical nuances and outcomes

Ashwin Viswanathan

Gaddum Duemani Reddy (none), Tarek Abuelem (none)

Introduction: Percutaneous cordotomy and myelotomy can be valuable for patients with intractable pain associated with malignancy. We describe our initial experience with the use of CT-guided destructive procedures.

Methods: A retrospective chart review was performed of patients who had undergone CT-guided cordotomy or myelotomy at The University of Texas M.D. Anderson Cancer Center between August 2011 and February 2012. CT-guided cordotomy was performed with a radiofrequency electrode (Cosman Medical, Inc.) applied to the C1-C2 level. CT-guided myelotomy was performed at T4 with a 16-gauge spinal needle used to create a mechanical lesion.

Results: Seven patients were included in this study (five males, two females). The median age at time of intervention was 35 years (range, 9-70). Six patients underwent percutaneous cordotomy and one underwent percutaneous myelotomy. Three of the seven patients expired during the study period, and the median postoperative survival was 31 days (range, 10 days - 6 months). For four patients, the intervention was successful as defined by clear functional improvements. Three patients had no functional improvement. There was one complication of postoperative mirror pain syndrome. No patients had worse pain or developed neurological deficits.

Discussion: Patient selection and pain pattern are the most critical determinants of a successful pain outcome. Careful entry point selection, impedance monitoring, and intraoperative testing can help to optimize surgical technique.

Conclusions: CT-guided destructive procedures are safe, and for the properly selected patient can lead to dramatic pain relief and functional improvements with low postoperative morbidity.

Pain therapies

Ventral striatal stimulation for chronic pain: Innovative care or clinical trial?

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Introduction: Stimulation of the anterior limb of the internal capsule / ventral striatum (ALIC/VS) has been investigated for the treatment of depression. Given the intimate involvement of the emotional system in pain, we are currently evaluating ALIC/VS DBS for deafferentation pain.

Methods: A phase I prospective, randomized, sham controlled, double-arm cross-over design clinical trial is underway to objectively assess the effects of deep brain stimulation of ALIC/VS stimulation in deafferentation pain. Separately, a compassionate care surgery was performed in a 29-year-old woman who presented with chronic, treatment-refractory facial pain secondary to facial surgery. Functional imaging was performed in both the maximum and minimum pain state. DBS electrodes were implanted with approval of the University Innovative Care Committee.

Results: Early results from intraoperative stimulation and single-blinded titration of DBS in the ongoing clinical trial suggest that ALIC/VS may be feasible for treatment-refractory central pain. In a compassionate care patient, subtraction PET imaging revealed metabolic changes in the ventral striatum corresponding with pain relief after ketamine infusion. She remains pain free at 3 month follow-up after ALIC/VS stimulation.

Discussion: The evaluation of new targets for DBS must be performed conscientiously. Competing interests of immediate clinical need vs. collection of generalizable data must be carefully weighed. Appropriate frameworks for novel DBS therapies, including committee review and performance of formal clinical trials, will be discussed.

Conclusions: It is imperative to differentiate treatment from research in the development of new surgical therapies. While single cases may benefit individual patients, they cannot provide generalizable data.

Pain therapies

Magnetoencephalography in Patients with Spinal Cord Stimulation for Reflex Sympathetic Dystrophy

Peter Pahapill

Wenbo Zhang (none)

Introduction: Pain is the most common complaint presenting to physicians for which there is no objective measuring tool or biomarker. Reflex sympathetic dystrophy (RSD) is a pain syndrome typically affecting a unilateral limb. Using magnetoencephalography (MEG), others have shown brain dysfunction corresponding to the affected RSD limb and its normalization with effective treatments such as medications or physical therapy. Spinal cord stimulation (SCS) provides effective treatment for RSD that is uniquely reversible and adjustable and has been thought to involve central nervous system (CNS) mechanisms. There have been no reports of MEG on pateints treated with SCS for any condition. Our goal was to determine the feasibility of documenting a correlation between the therapeutic effects of SCS and CNS changes as detected by MEG in RSD patients.

Methods: Two patients treated with thoracic or cervical SCS for their leg or arm RSD were studied with MEG. Baseline and tactile-evoked responses were recorded with and wtihout effective SCS.

Results: MEG recordings were safely obtained from patients with SCS systems with minimal interference. Preliminary analysis shows alterations in MEG recordings corresonding to the RSD limb that were affected by SCS therapy.

Discussion: We will discuss potential implications of these preliminary results, including the use of SCS and MEG as tools for developing biomarkers for pain and a better understanding of the CNS mechanisms of pain and SCS.

Conclusions: This is the first report of MEG in SCS patients. Recordings can be obtained safely with minimal interference.

Pain therapies

Anatomy and Physiology of the Dorsal Root Ganglion: New Developments

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Introduction: The dorsal root ganglion (DRG) has recently become a target of interest for the treatment of chronic, intractable neuropathic pain. This stems from the critical role the DRG plays in the development and maintenance of neuropathic pain.

Methods: We have reviewed the essential pathophysiology in primary sensory neurons underlying chronic neuropathic pain conditions, performed in vitro electrophysiologic investigations and correlated these findings with both recent clinical trial results examining epidural DRG neurostimulation as a potential therapy.

Results: Pre-clinical data confirms a hierarchy of pathophysiologic changes in DRG cells following injury which correlate with the development of neuropathic pain. These changes involve alterations in membrane excitability and ion channel expression and function which result in hyperexcitability of those DRG cells with primary sensory function involving the territory of injury. Activation threshold of these neurons decreases by approximately 50% following injury. In vitro experiments demonstrate that application of an electrical field across cells in the DRG can suppress this hyperexcitability suggesting a mechanism by which neurostimulation of the DRG can suppress pain. Clinical findings from ongoing clinical trials also support these observations.

Discussion: Both pre-clinical and clinical trial outcomes data suggest that neurostimulation of the DRG can provide reductions in pain, possibly by affecting primary sensory neuron function. This effect is specific for pain processing and also demonstrates important potential therapeutic benefits over currently existing therapies.

Conclusion: The results of these pre-clinical and clinical investigations suggest that DRG stimulation may be effective in alleviating chronic neuropathic pain.

Pain therapies

OCCIPITAL NERVE STIMULATION (ONS) FOR THE TREATMENT OF CHRONIC NEUROPATHIC HEADACHE

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Migraine is highly prevalent along with the high percentage of treatment-refractory cases. ONS may provide pain relief for patients with otherwise refractory primary headache disorders. It is more generally applicable than other invasive methods. We investigated ONS in a series of patients to determine efficacy, complications and outcome. We included a case series of 6 patients who had chronic headaches for a duration of 3.8 y who underwent ONS lead implantation (SJM, Octrode). Prior to surgery patients had received conservative and surgical therapies including antidepressants, occipital nerve blocks, opioids, cervical posterior fusion (one patient), without success. Three patients suffered from chronic migraine, one had a history of thalamic infarction, one patient suffered from cluster headache. Using a midline approach two octrodes were placed subcutaneously and positioned across the level of C1 using fluoroscopy. Leads were placed under general anesthesia and externalized for three days. All patients mentioned significant relief of pain, so that they all underwent insertion of the generator (eon MINI, SJM). Decreases in pain led to an improvement in functional capacity during the 3 months follow-up after implantation. The mean VAS score changed from 7.5 Â± 1.5 to 2.5 Â± 1.3 at the 3 months follow-up. No complications occurred.
The exact mechanism of neuromodulation effect in migraine treatment remains unclear. ONS appears to be both safe and efficacious for the treatment of medically intractable migraine headaches. Further investigations are required to evaluate criterias for patient selection, stimulation targets and parameters and device programming, and further improve clinical results.

Pain therapies

Mechanism of Therapeutic Benefit with Dorsal Column Stimulation Using a Computational Model of the S

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Jay L. Shils, PhD (none), Kris W Carlson (none), LZ Mei (none)

Introduction:
Stimulation of axons within dorsal columns of the human spinal cord has become widely used therapy to treat refractory neuropathic trunk and limb neuropathic pain as well as other conditions. The mechanisms by which such stimulation achieves pain relief, have yet to be fully elucidated and better understanding may lead to more effective use of the therapy.

Methods:
A computational model of three levels of the lumbar enlargement region in the human spinal cord involving over 300,000 individual neurons and over 42 million synapses was developed. The overall parameter space of the model circuitry was validated by reproducing well known reflex arcs (eg. H-reflex). In addition both a simulated â€˜painâ€™ signal with topographically activated isolated c-fiber regions and a â€˜ SC stimulationâ€™ field with topographically activated Ia fibers in the dorsal columns were modeled.

Results:
The â€˜painâ€™ signal drives analogous regions of laminae II and V wide-dynamic range (WDR) neurons while the â€˜stimulationâ€™ signal generated spatially select inhibition that ameliorated the pain-induced activity in the WDR cells. This effect was both amplitude and spatially selective.

Discussion:
The subject model, the most sophisticated human spinal cord model yet created, allowed hypotheses regarding pain relief mechanisms to be tested and compared to clinical SCS therapies. Specific dynamic activity of spinal cord neurons is typically impossible to study by other means.

Conclusion:
Future use of this complex dynamic computational model of the human spinal cord will allow further complex stimulation paradigms to be evaluated and understood prior to testing in patients.

Psychiatric diseases

Deep Brain Stimulation (DBS) for Treatment-Resistant Depression: A Randomized Controlled Trial

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Deep Brain Stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) for Treatment-Resistant Depression (TRD) has been investigated in previous open-label studies. We now report the outcomes of a randomized, prospective, double-blind controlled multi-center feasibility trial of VC/VS DBS for TRD.

Methods: Thirty subjects across five centers with severe, TRD underwent bilateral implantation of Medtronic 3391 leads in the VC/VS. Target coordinates were 5-10 mm from midline, 0-5 mm anterior to AC, and 1-4 mm ventral to AC. The leads were connected to Kinetra IPGs. Active or sham stimulation was delivered during a 4- month blinded phase, followed by open stimulation continuation phase. The primary outcome measure was proportion of responders (>50% improvement on Montgomery-Asberg Depression Rating Scale (MADRS)) at the 4-month endpoint.

Results: Of 30 subjects randomized (mean current depressive episode 11.4 years; mean baseline MADRS 36.7 + 4.3), 29 completed the blinded phase. 3/15 subjects (20%) responded to active and 2/14 (14.3%) responded to sham stimulation. Mean MADRS reduction was 19.6% for active and 24.6% for sham stimulation (p=0.34). Complications included 5 infections (3 requiring explant), 1 asymptomatic hemorrhage, 1 lead revision and reversible stimulation related events. Active contact location did not appear to correlate with clinical outcomes.

Discussion: Study variables of patient selection, targeting, and programming will be discussed in the context of the blinded and longer-term outcomes.

Conclusion: DBS of the VC/VS for TRD was not superior to sham stimulation in a 4-month randomized, controlled trial. However, improvements in some subjects were noted in the continuation phase.

Psychiatric diseases

Stereotactic Ablative Surgery for the Treatment of Refractory Depression

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Introduction: Major depression (MD) is the most prevalent psychiatric disorder, affecting at least 5% of the world population. Most authors agree that 10-20% of the patients are refractory to the best conservative management. In these cases, surgery may be contemplated. Ballantine Jr et al (1965) were the first to use an ablative procedure for the treatment of MD (anterior cingulotomy). Since then, other procedures have been used, such as anterior capsulotomy, subcaudate tractotomy and limbic leucotomy (LL). Mayberg and Lozano (2005), on the other hand, were the first to perform DBS to treat this disorder (subgenual cingulum DBS). Other targets (ventral capsule/nucleus accumbens and inferior thalamic peduncle) are also effective. We here present our series of five patients in whom we performed bilateral LL+subgenual cingulotomy.

Methods: Five patients, 3M/2F, mean age of 31 years, presenting with refractory MD were operated on. Three of them were previously submitted to ECT, and two presented concomitant OCD. Preoperative assessment included MR, SPECT, and neurological/neuropsychological/psychiatric evaluations. The severity of the disease was rated using the HDS and/or the BDI. Targetsâ€™ coordinates were obtained from IR coronal/axial MR, CT-scan and image fusion. Macrostimulation was performed before lesioning in all cases.

Results: Postoperative MR was performed in all patients, confirming adequate lesion placement. No surgical complications were observed. All patients derived excellent (>70%) relief of their symptoms, which persisted after a mean follow-up of 27 months.

Discussion and Conclusions: LL+subgenual cingulotomy seem to be a safe and very effective technique to treat of refractory MD.

Psychiatric diseases

Fornix DBS for Alzheimer's Disease: Neuronal activation, Cerebral Metabolism, and Clinical Outcome

Dr. Adrian W. Laxton
(University Grants/Research Support, Company: NREF Fellowship from AANS; Krembil Neuroscience Discovery Fund)

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Introduction: Alzheimerâ€™s disease (AD) is characterized by impairment in the neural elements and circuits underlying cognitive and memory functions. We hypothesized that fornix deep brain stimulation (DBS) could modulate neurophysiological activity in these pathological circuits and possibly produce clinical benefits.

Methods: We conducted a phase I trial of fornix DBS in 6 patients with early AD. Three lines of investigation were pursued: (1) mapping stimulated brain areas , (2) assessing DBS effects on cerebral glucose metabolism, and 3) measuring DBS effects on cognitive function.

Results: Acute stimulation produced ipsilateral time-dependent activation of mesial temporal then lateral temporal and parietal neocortical areas. DBS increased cerebral glucose metabolism in pathologically relevant regions. These increases were correlated with better clinical outcomes. Clinical outcome measures suggested possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients. There were no serious adverse events.

Discussion: DBS offers the possibility of modulating specific cognitive and memory circuits, and it appears that this approach can be safe. These safety and biological effects are sufficiently compelling to warrant a more thorough appraisal of the possible therapeutic benefits of this strategy in AD.

Conclusions: Persistent cortical metabolic increases after one year of DBS were associated with better clinical outcomes in this patient sample and are greater in magnitude and more extensive than the cortical circuitry effects reported for pharmacotherapy over one year in AD.

Psychiatric diseases

Bed Nucleus of Stria Terminalis and Nucleus Accumbens DBS for Depression

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(Other Financial or Material Support, Company: Medtronic financial support of study (DBS hardware))

Dr Rebecca Segrave (none), Dr Sally Herring (none), Professor Paul Fitzgerald (Disclosure: Other Financial or Material Support Company: Medtronic financial support of study (funded hardware))

Introduction:
Deep brain stimulation (DBS) is being increasingly used to treat depression, however the optimal target is unclear. We evaluated intraoperative responses and long-term outcomes following DBS of the nucleus accumbens (NA) and bed nucleus of stria terminalis (BNST) for treatment-resistant major depression.

Methods:
Five females (age 27-60 yrs) with a major depressive disorder of at least several years duration and an MADRS score of >25 participated. Approval was obtained from the Victorian Psychosurgery Review Board and our Institutional Ethics Committee. Medtronic 3387 electrodes were implanted bilaterally in the NA (n=1) and BNST (n=4) under local anaesthesia. Intraoperative stimulation responses were recorded. Mean follow up was 21 months (12-45 months).

Results:
A)Positive and negative mood effects could be induced intra-operatively at the more posterior site (BNST). There was a trend for more beneficial DBS-related effects at the more proximal electrodes, and more negative effects with distal stimulation. The pattern varied markedly between patients.
B)Outcomes: At follow up, 2 patients were in remission (40%), two had a â‰¥50% response (40%), and one had a <50% response (20%). Mean reduction in MADRS was 57% (range 15-93%) and BDI-II was 64% (8-92%). There were no complications.

Discussion:
These results support further study of the BNST as a DBS target for depression. Further evaluation of intraoperative responses may allow refinement of electrode placement, simplify programming, and improve outcomes.

Conclusions:
Intraoperative BNST stimulation can induce acute mood changes. The BNST appears to be a promising DBS target for treatment-resistant depression, and warrants further investigation.

Psychiatric diseases

Radiosurgical Neuromodulation for Treatment Resistant Depression in a Setting of Bipolar Disease

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Charles DeBattista (none), David Speigel (none), Hugh Brent Solvason (none), Jessica Hawkins (none), Scott G. Soltys (none)

Objective: Treatment resistant depression is not uncommon in a setting of bipolar depression (BD). Recent studies implicate over-activity within Cingulate gyrus 25 (Cg25). We present early data from a Phase I pilot study suggesting that non-ablative Radiosurgical Neuromodulation (RSN) targeting of Cg25 is safe and possibly useful in the treatment of refractory depression.

Methods: After three years of regulatory wrangling, an investigator-initiated IDE was obtained. Eligibility required a failure of 4 antidepressants and ECT. Informed consent included an independent assessment of competence. Patient evaluation included a comprehensive psychological battery as well as both PET and MRI. Bilateral target volumes, measuring ~70 mm3, were located within Cg25 using imaging landmarks described by Mayberg (2009). RSN was administered via CyberKnife using a Dmax of 75 Gy and a 60 Gy marginal dose (80%). To assess safety, serial neuropsychological, clinical and imaging evaluations were performed.

Results: Follow-up of the three subjects was 3, 12 and 24 months. One week following RSN, the first two experienced dramatic symptom relief documented on formal testing. This benefit remained largely durable during the first year of follow-up. The third patient had significant subjective improvement which could not be documented on formal testing. MRI and PET scanning revealed no evidence of any structural or functional lesions within Cg25.

Conclusions: Early results suggest that RSN administered to Cg25 is safe and possibly effective in treating refractory BD. If the present results hold up to further scrutiny, RSN could represent a useful tool for down-regulation of some pathological brain circuits.

Psychiatric diseases

Grading refractory anorexia nervosa for surgical treatment

Bomin Sun

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Introduction: To grade anorexia nervosa as a reference of patient and surgical procedure selection for surgical treatment based on the surgical results and clinical characteristics of anorexia nervosa.

Methods: 104 patients with refractory anorexia nervosa underwent bilateral deep brain stimulation of nucleus accombance or/and bilateral anterior capsulotomy. 61 patients were followed up over 12 months. Body mass index (BMI) and menstrual status , Yale-Brown obsessive-compulsive rating scales, Hamilton Anxiety rating scales and Hamilton depression rating scales were employed to evaluate the efficacy pre and 1 year post-operatively. Based on the clinical characteristics and surgical results of anorexia nervosa, patients were graded from I to IV.

Results:12 cases of grade II patients were cured, 4 of them were treated by bilateral NAcc DBS only, the other 8 cases by bilateral capsulotomy. 18 cases of grade III were significantly improved or cured, 5 of them underwent bilateral capsulotomy after failed DBS, the others were treated by capsulotomy only. In 31 cases of grade IV, 25 cases were significantly improved or cured; 5 cases with mild improvement or no change, 3 of these 5 cases were treated by DBS plus capsulotomy; 1 case suicided 9 months after capsulotomy due to severe depression even her BMI recovered.

Discussion: For grade II refractory anorexia nervosa patients, both DBS and anterior capsulotomy are effective, grade III patients are mildly responsive to DBS and should be treated by bilateral capsulotomy. The surgical efficacy of Grade IV patients was not as good as grade II and III.

Conclusion:Grading of anorexia nervosa is very important for patient and surgical procedure selection.

Psychiatric diseases

NEUROANATOMICAL PREDICTORS OF RESPONSE TO DEEP BRAIN STIMULATION FOR TREATMENT RESISTANT DEPRESSION

Tejas Sankar

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Introduction: Deep brain stimulation (DBS) of the subcallosal cingulate gyrus (SCG) improves the symptoms of refractory depression in some patients but not others. We hypothesized that there are pre-existing structural differences between the brains of responders and non-responders to SCG DBS, detectable using conventional, pre-operative structural magnetic resonance imaging (MRI) scans.

Methods: We studied pre-operative, T1-weighted MRI scans of twenty-five patients treated with SCG DBS within the last eight years at the Toronto Western Hospital. Responders (n=14) were patients whose 12-month Hamilton Rating Scale for Depression (HAMD-17) score improved by >50% from baseline prior to DBS. A trained observer blinded to patient identity measured the pre-operative volume of the SCG region in each patient. Automated measurements of hippocampal, thalamic, whole-brain, total grey matter, and total white matter volume were obtained. Automated whole-brain cortical thickness analysis was also performed.

Results: Baseline SCG and thalamic volumes were significantly larger in patients who responded to DBS. Hippocampal volume did not differ between groups. Interestingly, grey matter volume across the entire brain was significantly higher in non-responders, and the ratio of pre-DBS grey:white matter volume distinguished between eventual responders and non-responders with high sensitivity and specificity.

Discussion: Greater structural integrity of the target SCG region may correlate with response to DBS, while non-response may be related to a developmental phenotype in which the structure of the whole brain is affected.

Conclusions: There are indeed structural differences between the brains of depressed patients who respond to SCG DBS and those who do not.

Psychiatric diseases

Brief electrical stimulation of the amygdala in rats enhances memory for specific events

David I. Bass

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Introduction: Emotional activation of the amygdala enhances memories for arousing events, and therefore investigating how the amygdala modulates memory can provide insights into memory enhancement with clinical relevance for certain neuropsychiatric disorders.

Methods: Rats were given a novel object recognition memory task in which they encountered a series of objects 30-45sec apart. Immediately following some of these encounters, rats received brief, unilateral, electrical stimulation to the amygdala. Memory for objects was tested either immediately following the study phase or 1 day later. In a separate experiment, stimulation was delivered to the left or right amygdala of an awake, behaving rat while field potentials were recorded along the hippocampus, which supports memory for events.

Results: Behavioral results indicated that memory for objects followed by amygdala stimulation was unaffected soon after the encounter, but memory for these objects was selectively enhanced 1 day later. Evoked potentials were recorded in the ipsilateral temporal hippocampus 5ms following each pulse to the amygdala, but were not observed contralaterally or in the ipsilateral septal hippocampus.

Discussion: The results indicated that precisely timed activation of the amygdala selectively enhanced memory for individual events. Memory enhancement may be achieved through projections to the ipsilateral temporal hippocampus, and therefore stimulating this pathway may be clinically relevant for cognitive disorders such as Alzheimerâ€™s disease, while inhibiting this pathway may be relevant to treating post-traumatic stress disorder.

Conclusion: Our findings demonstrate that direct activation of the amygdala selectively enhances memory, possibly via projections from the amygdala to the ipsilateral temporal hippocampus.

Psychiatric diseases

Deep brain stimulation for Obsessive-Compulsive Disease: Is the side relevant?

Juan A. Barcia

Javier Saceda (none), JosuÃ© Avecillas (none), Juan J. LÃ³pez-Ibor (none), Julia GarcÃ-a-Albea (none), Laura Reyes (none), MarÃ-a InÃ©s LÃ³pez-Ibor (none), RocÃ-o Arza (none), Rosa YÃ¡Ã±ez (none), TomÃ¡s Ortiz (none)

Introduction. Deep brain stimulation for obsessive-compulsive disease (OCD) has targeted several subcortical nuclei, including STN and Nucleus Accumbens. While the most appropriate target is still being searched, little attention has been given to the side of the stimulated hemisphere in relationship to outcome.

Methods. We report 2 cases of patients diagnosed with OCD, one having symmetry obsessions and the other one with sexual-religious obsessive thoughts. They were implanted bilaterally with deep electrodes located at both STN and Nuclei Accumbens. The effectiveness of the stimulation was tested for every possible paired combination of electrodes guided by the YBOCS score.

Results. The combination of electrodes which best relieved their symptoms was both the left STN and left accumbens. In case 1, Preoperative YBOCS was 33 and after activating the best combination it scored 16. All other possible combinations scored from 28 to 20, the lower scores always including one of the left electrodes. Case two scored an YBOCS of 33 preoperatively and 12 after both left electrodes stimulation (range 15-18). The patient has now a stable YBOCS of 3 and reports to be free of obsessions.

Discussion. Other reports have sustained that stimulation only of right side reliefs OCD symptoms. However, fMRI shows that different OCD dimensions recruit different cortical areas, and this may lead to different striatal targets individualized for each patient. This concept possibly applies to the site of stimulation. This result has led us to change our OCD DBS protocol.

Conclusions. Probably each patient has an individualized target including the side to stimulate.

Psychiatric diseases

Modulation of Limbic Circuitry by Nucleus Accumbens DBS in a Large Animal Model: an fMRI study

Emily Knight

Emily Knight (none), Hoon-Ki Min (none), Inyong Kim (none), Kendall H. Lee (none), Michael Marsh (none), Osama Abulseoud (none), Sun-Chul Hwang (none)

Introduction

Nucleus accumbens (NAc) DBS has been used clinically for the treatment of psychiatric disorders, including obsessive-compulsive disorder, treatment resistant depression, alcohol dependence, anorexia nervosa and Touretteâ€™s syndrome. However, the mechanism underlying the therapeutic benefit of DBS including the brain areas that are activated and the neurochemical correlates, is largely unknown. Here, we utilized 3.0T functional Magnetic Resonance Imaging (fMRI) changes in Blood Oxygenation Level-Dependent (BOLD) signal to test the hypothesis that NAc DBS results in site-specific activation of the neural structures within the limbic circuitry complex distant from the electrode site in a large animal (pig) model.

Methods

Pigs (n=8) were stereotactically implanted in the NAc with Medtronic 3389 electrodes and received DBS (1-7 V, 60-130 Hz, and pulse widths of 100-500 Î¼sec). The regions of stimulation evoked BOLD signal change were evaluated using an echo planar imaging (EPI) sequence.

Results

We observed clear stimulation time locked activation in the ipsilateral prefrontal (n=6 pigs), insula (n=4 pigs), caudate (n=3 pigs) and cingulate (n=3 pigs) that was stimulation frequency and voltage dependent. Interestingly, decrease in fMRI BOLD signal was also observed in the caudate (n=4 pigs) and cingulate (n=1 pig).

Discussion and Conclusion

Our results support the hypothesis that NAc DBS results in site-specific activation of the neural structures within the limbic circuitry complex. Specifically, NAc DBS results in modulation of activity in areas distal to the electrode site, notably the prefrontal cortex, cingulate, and insula, which may underlie the therapeutic effect of NAc DBS in psychiatric conditions.

Radiosurgery

Fractionated Stereotactic Radiosurgery For Cerebral Metastases: Tumor Control

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INTRODUCTION. Single session treatments have been the mainstay of stereotactic radiosurgery (SRS) for patients with metastatic cerebral tumors. However, patients with tumors that are large and/or in eloquent locations may not be candidates for this method. Alternatively, multiple session SRS may confer radiobiologic treatment advantages in the eradication of metastatic cerebral tumors. We compared the results of single and multiple session SRS for metastatic tumors.

METHODS. We reviewed all patients from our institution who were treated with SRS for cerebral metastases between January 2010 and December 2011. Collected data included diagnosis, tumor location, lesion volume, and SRS dose.

RESULTS. 132 patients with 249 lesions underwent SRS. 177 lesions (71%) were followed from 407 serial MRI scans ranging from 0.2 â€“ 28.2 months (6.19 Â± 5.95 months). 53 lesions had treatment volumes greater than 3 cc. Of these, 29 lesions underwent single session SRS and 24 were treated in 3 sessions. Median prescription doses for single and multiple SRS were 18 and 24 Gy, respectively. Tumor progression was noted in 8 lesions from 7 patients treated with a single session, compared with progression in only 1 lesion treated with 3 sessions. Lesion volume following multiple session SRS decreased by 53%, vs. 15.5% after single session ($p = 0.02$).

DISCUSSION. Multiple session SRS for patients with large brain metastases yielded improved local tumor control compared with single session SRS.

CONCLUSION. These preliminary results have encouraged us to continue evaluating the efficacy of multiple session SRS for patients harboring large cerebral metastases.

Radiosurgery

Synchrontron-Generated Microbeam Cortical Transections

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Introduction
Synchrotron-generated microbeams have been used to create cortical transections

Methods: Cortical transections were generated in the left motor cortex of healthy Wistar rats by the delivery of a microbeam array carrying incident doses up to 330 Gy . Three different microbeam size were tested (25, 60 and 100 micron).We also tested the ability of microbeam transections to stop the seizures induced by kainic acid .

Results: No neurological deficit was observed after the placement of microbeams sensorimotor cortex transections The rats gained weight regularly and were sacrificed after 7 months, having shown no signs of motor impairment contralateral to the transections. Immunohistochemical analysis confirmed the presence of neuronal loss and mild reactive gliosis along the beam penetration paths in the left motor cortex. Kainic acid injection into the left motor cortex induced severe convulsive seizures in the control rats, lasting on average 42 hours (range:18-72 hours). Seizure duration was substantially reduced in the rats undergoing transections as compared to the controls. Evident seizures disappeared after an average of 180 (3 rats receiving high doses) and 200 minutes (3 rats receiving low doses) in the group of 6 rats treated with 100 micron beams. The same result was observed in the other group of 6 rats treated with 600 micron beams, with seizures disappearing after an average of 130 (3 rats receiving high doses) and 160 minutes (3 rats receiving low doses).

Discussion: Cortical transections induced by synchrotron-generated microbeamas are well tolerated and induce seizure relief.

Technology transfer

Intraoperative MRI guidance for laser interstitial thermal therapy

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Introduction. Laser interstitial thermal therapy (LITT) has been described as a treatment for patients with refractory brain tumors. Low-field intraoperative MRI (iMRI) was assessed as a tool to guide laser placement.

Methods. Five patients were treated with iMRI-guided LITT. Two patients had tumors in the brainstem, one had a prolactinoma, and two had cerebral metastatic tumors. Each patient had progressive symptoms from tumor growth, despite maximal attempts at prior surgery, radiation therapy or radiosurgery, and chemotherapy.

Laser fibers (Visualase, Houston, TX) were stereotactically placed in the operating room under guidance with a 0.15 Tesla (T) intraoperative MRI. Patients were transferred to a 1.5T MRI for LITT. Laser therapy was administered until ablation zones reached desired sizes or critical structures exceeded preset safety limit temperatures. Contrast-enhanced T1 weighted MRI was then done to confirm the volume of treatment.

Results. IMRI ultimately confirmed accurate laser placement in the operating room before transfer to diagnostic MRI for LITT in all patients. In 1 patient with a medial parietal metastatic tumor, surgical navigation without intraoperative imaging resulted in laser misplacement; this patient underwent a successful 2nd procedure with iMRI guidance. Suboptimal placement also was noted in a patient with epilepsy, who had a laser fiber aimed towards his hippocampus without iMRI.

Discussion. Successful completion of LITT is facilitated by the use of iMRI guidance. This ensures accurate laser insertion into the tumor and subsequent technically successful tumor ablation

Conclusion. Surgical navigation alone without iMRI can result in fiber misplacement and an aborted LITT procedure.