Oral Presentations

101 Incidence of Seizures Induced by Intracranial Research Stimulation: a Multicenter Prospective Study in 770 Sessions Across 188 Patients

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Introduction

Patients with epilepsy undergoing intracranial recordings provide an increasingly utilized opportunity to study human neurophysiology. Intracranial stimulation in these patients for research purposes can provide unique and valuable information, but ethical concerns demand a thorough appreciation of the associated risks. We measured the incidence of stimulation-associated seizures in a large multi-institutional prospective study using consistent stimulation parameters and seizure monitoring criteria.

Methods

188 subjects who underwent intracranial epilepsy monitoring across 10 institutions participated in 770 stimulation sessions over 3.5 years. Seizures within 30 minutes of a stimulation session were considered stimulation-associated. We analyzed stimulation parameters, seizure incidence, and typical seizure patterns.

Results

In total, 14 seizures occurred during or soon after a stimulation session (1.8% of sessions). Six seizures were similar to the patient's typical seizures in terms of semiology, onset, and spread. All events were single seizures. The majority were simple partial (64%), or complex partial (29%); only one was generalized. No adverse events occurred, and length of stay in the monitoring unit was not affected. The mean amplitude of seizure-associated stimulation was 1.125mA (range 0.25-2mA), compared to a mean amplitude of 1.055mA (range 0.1-3.5mA) delivered in sessions without seizures. Duration and frequency ranged from 0.25-4.6 seconds, and 10-200Hz, respectively.

Conclusions

Seizures are a known possible risk of intracranial research involving brain stimulation. Our observed rate of 1.8% likely overestimates the true risk, as some seizures may have occurred coincidentally around the time of stimulation sessions. Stimulation-associated seizures did not add morbidity or affect the clinical course of any patient. These results will be important for understanding the feasibility and safety of intracranial stimulation for research purposes.

102 Tuning Direct Electrical Amygdala Stimulation Parameters for Declarative Memory Enhancement in Humans

Cory S. Inman; Joseph Manns; Kelly R. Bijanki; David Ian Bass; Stephan Hamann; Daniel Drane; Rebecca Fasano; Robert E. Gross; Jon Timothy Willie

Introduction
We have previously demonstrated that brief electrical stimulation to the basolateral amygdala (BLA) reliably enhances memory in humans without eliciting an emotional response (Inman et al., 2018). The present study examined whether human amygdala stimulation immediately following the presentation of neutral object images enhanced later declarative memory and the effects of various stimulation parameters on later declarative memory.

Methods
We recruited over 27 epilepsy patients undergoing intracranial EEG (iEEG) with depth electrode contacts placed in the BLA and sub-regions of the medial temporal lobe (MTL). During continuous iEEG, each participant was presented a series of photographs of neutral objects, some of which were followed immediately by stimulation to the amygdala (8 trains of 50-Hz pulses). In further experiments, we manipulated stimulation amplitude (0.5-3.5 mA), duration (1-3 sec), and location (BLA or MTL sub-region) across subsets of patients to determine whether any stimulation parameters might boost the original memory enhancement effect. Recognition and free recall memory was tested immediately after the study session and the following day.

Results
Across all patients and stimulation parameters, participants recognized neutral objects initially followed by amygdala stimulation more accurately than control objects during the one-day test. Increasing stimulation amplitude and duration did not further enhance memory compared to original stimulation conditions during the one-day test. Stimulating other MTL sub-regions (e.g. hippocampus), with the same parameters as prior BLA stimulation experiments produced an impairment of memory for stimulation-paired objects. Notably, accurate recognition of stimulated objects elicited oscillatory activity between the BLA, hippocampus, and perirhinal cortex that resembled the prior stimulation pattern.

Conclusions
Human amygdala stimulation prioritizes event-specific declarative memories into long-term storage, the recollection of which is associated with a distinct electrophysiologic signature of prior stimulation. With further tuning, amygdala stimulation may provide a novel therapeutic intervention for memory disorders through selective enhancement of specific memories.

103 A Cellular Substrate for Theory of Mind in the Human Prefrontal Cortex

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Introduction

Theory-of-mind refers to our ability to form a complex understanding of the world and reason about the beliefs of others and understand that others may have beliefs that differ from our own. The capacity to build a detailed model of another's intrinsic representation of the world is thought to be among the most advanced features of human cognition. Its dysfunction is also a major source of many psychosocial disorders such as autism. How these computations are formulated by single neurons in humans is unknown.

Methods

We recorded from single units in the dorsal prefrontal cortex (dPFC) an area implicated in inferential processing in humans undergoing deep brain stimulation surgery. Participants were read complex narratives about real-world scenarios and were required to formulate ideas about the individuals and events within them. Single-unit and population-level Fisher discriminant analysis was used to test context-specific neuronal encoding of the state (true versus false) of other's (characters in the narratives) beliefs.

Results

A total of 212 single units were recorded from 11 participants. Using dynamic population decoding, we find that the activity of many neurons reflected inferences made about the other's beliefs. A total of 49 (23.1%) neurons responded to variations in the other's beliefs and distinguished another's false beliefs from the participant's own. Moreover, when considered together, the neurons were highly predictive (74% of trials correct) of another social agent's state of belief.

Conclusions

Collectively, these observations reveal a cellular process that may allow humans to construct a detailed mental representation of others and reason about their intrinsic beliefs. These computations could provide a cellular framework for human theory-of-mind, and offer insight into the mechanism by which the prefrontal cortex allows us to formulate complex concepts about the world and how its dysfunction leads to cognitive impairment.

104 High Degree-of-freedom Movement by a Person with Paralysis Using an Implanted Brain-computer Interface

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Introduction

Brain-computer interfaces (BCIs) are being developed to restore movement to people with paralysis. BCIs decode cortical activity to infer movement intentions, providing an intuitive way to command complex movements. A pressing goal is to accurately and simultaneously control the many degrees-of- freedom (DOFs) of an arm.

Methods

A BrainGate2 clinical trial participant with tetraplegia had two 96-electrode arrays implanted in left motor cortex. He imagined manipulating an object with right arm movements and commanded 'grasps' with attempted left bicep contractions. Neuronal firing rates were decoded using a high DOF extension of the ReFIT + HMM decoding algorithm from [Pandarinath et al., eLife 2017]. To rigorously quantify high-DOF neural control quality, we first conducted experiments in a virtual reality environment, thus eliminating the added variability of physical effectors. The tasks required moving a virtual object to a specified location and then holding or grasping there. Decoders calibrated in this environment were then used to move a real robotic arm.

Results

The participant was able to perform a 4 DOF object movement task (3D translation and 1D rotation), acquiring 22.6 targets per minute with a path efficiency of 0.76 (where 1 denotes perfectly direct movements to the target). These metrics were similar across target subsets requiring position change along 1, 2, 3 or all 4 DOF. This demonstrates distinct and specific control of each DOF, and simultaneous control of all DOF?. Practical application of this capability was subsequently demonstrated by using the same decoders, plus a binary grasp toggle, to perform a modified box-and- blocks and a bottle pouring task using a robotic arm.

Conclusions

Simultaneous and intuitive control of multiple movement DOFs despite the limitations of current generation neural sensors demonstrates encouraging progress towards the goal of restoring independence to people with paralysis.

105 INTREPID: A Prospective, Double Blinded, MultiCenter Randomized Controlled Trial Evaluating Deep Brain Stimulation with a New Multiple Source, Constant Current Rechargeable System in Parkinson's Disease

Philip A. Starr; Paul A. House; Roshini Jain; Lilly Chen; INTREPID Clinical Study Group; Jerrold L. Vitek

Introduction

Deep Brain Stimulation (DBS) is effective for treatment of the motor signs and fluctuations associated with Parkinson's disease (PD). Although DBS efficacy has been substantiated by several randomized controlled trials, the degree of improvement varies significantly. Needs for further innovation in DBS devices have existed for the last 25 years. The INTREPID Study assessed improvement in motor function and quality of life in patients with advanced, levodopa-responsive PD following bilateral, sub-thalamic nucleus (STN) DBS using a new device capable of multiple independent current sources that allowed for selective activation of individual contacts on the DBS lead thereby permitting a defined distribution of applied current.

Methods

INTREPID is a multicenter, prospective, double blinded, randomized controlled trial (RCT) sponsored by Boston Scientific. Subjects with advanced PD were implanted bilaterally in the subthalamic nucleus (STN) with a multiple source constant current DBS System (Vercise, Boston Scientific). Blinded subjects were randomized to either receive active vs. control settings for a 12 week period. All assessments were completed by a blinded assessor. Following the blinded period, subjects were programmed to receive best therapeutic settings. Improvement in motor function and quality of life was evaluated using a PD diary, UPDRS, PDQ-39, and a battery of neuropsychological assessments. Adverse events were recorded.

Results

The study successfully met the primary endpoint ($p < 0.001$) with a mean difference of 3.03 ± 4.2 hrs. from baseline to 12 weeks between the active and control groups in ON time (PD diary), with no increase in antiparkinsonian medications. The study also met several of the secondary endpoints. The incidence of infection was 2.7% and peri-operative intracranial hemorrhage was 1%. The safety profile is similar to published reports.

Conclusions

The results of the INTREPID Study demonstrate use of a multiple-source, constant-current DBS System is safe and effective in the treatment of Parkinson's disease symptoms.

106 Dorsal Anterior Cingulum Bundle Stimulation Produces Positive Affect, Anxiolysis Without Sedation, and Analgesia in Twenty Patients

Kelly R. Bijanki; Cory S. Inman; John Gale; Daniel Drane; Helen S. Mayberg; Jon Timothy Willie

Introduction

We sought to elucidate the mechanism of positive affect, anxiolysis, and analgesic responses evoked by the application of direct electrical stimulation to the anterior cingulum bundle in twenty patients.

Methods

Patients with treatment-refractory epilepsy underwent stereotactic depth electrode (AdTech SEEG) implantation for seizure focus localization. Stimulation testing occurred extraoperatively during the intracranial monitoring phase, where electrical stimulation was delivered via a current-controlled cerebral stimulator. Stimulation did not cause after-discharges or epileptiform activity. Subjective effects of stimulation were recorded via video, and objective effects were quantified in terms of local field potentials, autonomic responses, and shifts in affective bias, a cognitive proxy for emotional state. In the index patient, stimulation produced anxiolysis without sedation and facilitated ongoing language testing during awake resection in the dominant temporal lobe.

Results

Stimulation was observed to evoke involuntary laughter and smiling, as well as patient-reported happiness, relaxation, and analgesia. Video analysis using machine learning revealed significant changes in facial motor dynamics under sham vs. subthreshold vs. suprathreshold stimulation. Further, stimulation was accompanied by a significant positive shifts in emotional bias ($p=.023$), and electrophysiology showed significant stimulation-evoked reductions in endogenous 6-11hz power and coherence following active stimulation ($ps < 0.0001$). Systematic examination of neuroimaging and behavioral responses clarified the critical aspects of cingulum bundle vs. frontal projection fiber engagement, as well as orientation of bipolar stimulation (parallel vs. orthogonal to the bundle) for evoking effects similar to those observed in the index case.

Conclusions

The current findings suggest the cingulum bundle as a target for mood and anxiety disorders, as well as chronic pain syndromes. Further, the novel application of cingulum stimulation in the index patient to evoke sense of well-being and anxiolysis without sedation during awake resection suggests a novel approach for facilitating such procedures.

107 Subthalamic Nucleus Deep Brain Stimulation Combined with Duloxetine Changes Pain Behavior in Parkinsonian Rats

Julie G. Pilitsis; Miriam M. Shao

Introduction

Chronic pain is the most common non-motor symptom in Parkinson's disease (PD) and is undertreated in half of PD pain cases (1). Subthalamic nucleus deep brain stimulation (STN DBS) relieves PD pain temporarily. To optimize STN DBS, we have combined it with duloxetine and shown increased mechanical thresholds indicative of antinociception in the hemiparkinsonian 6-hydroxydopamine (6OHDA) lesion rat model (2). In this study, we advance from investigating STN DBS-duloxetine's effects on nociception to quantifying its effects on pain-related behavior in the place escape/avoidance paradigm (PEAP).

Methods

Male seven-week-old Sprague-Dawley parkinsonian rats were treated with STN DBS, duloxetine, or STN DBS-duloxetine. Rats underwent PEAP testing before and after treatment in a chamber consisting of a bright and dark side that were both easily accessible. When rats spent time in the dark side, they were poked with a suprathreshold (60.0 g) von Frey filament on their left/parkinsonian neuropathy-affected hind paw; in the bright side, rats were poked on their right/non-parkinsonian hind paw. Because rats inherently prefer dark environments, time spent in the bright side represented pain-related escape/avoidance behavior. Percent changes were calculated for bright side times before and after treatment, and data was analyzed using one-way ANOVA.

Results

Percent decrease in bright side time was significantly greater after STN DBS-duloxetine than after STN DBS ($p=0.031$) and duloxetine alone ($p=0.036$). STN DBS-duloxetine decreased bright side time by $32.82 \pm 7.62\%$ ($n=4$), while STN DBS ($4.17 \pm 11.55\%$, $n=4$) and duloxetine ($1.22 \pm 10.61\%$, $n=5$) caused minimal percent bright time changes. Therefore, STN DBS-duloxetine reduced pain-related behavior significantly more than STN DBS and duloxetine alone.

Conclusions

Our project presents STN DBS-duloxetine as a new treatment for PD pain. Because escape/avoidance behavior has been associated with the anterior cingulate cortex (ACC) (3), STN DBS-duloxetine's mechanism may involve altering ACC neuronal activity in the descending inhibitory pain pathway.

108 Prominent Temporal Coding of Cognitive Control in Human Prefrontal Cortex

Guillermo Horga; Sameer A. Sheth; Garrett P. Banks; Mark Yates; Yagna Pathak; Guy McKhann; Elliot Smith

Introduction
In our daily lives, we are constantly faced with situations requiring us to make rapid yet accurate decisions. These elements of "cognitive control" are considered critical components of normal cognition, and deficiencies in these processes underlie several neuropsychiatric disorders. Many studies have broadly attributed these cognitive control processes to prefrontal cortex, yet little is known about their neurophysiological basis.

Methods
We recorded neuronal firing rates and local field potentials (LFP) from the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (dlPFC) in 19 patients undergoing neurosurgical procedures requiring intracranial electrodes, including epilepsy monitoring (N=12) and DBS (N=7). Subjects performed a Stroop-like task with 4 categories of decision conflict.

Results
Neurons in both dACC (N=136) and dlPFC (N=367) demonstrated sparse firing rate coding of conflict level (dACC: 10.3%, dlPFC: 4.1%) (Figure 1). On the other hand, a majority of neurons encoded conflict level using a temporal code consisting of spike-field coupling in beta and theta (dACC: 49%, dlPFC: 52%). Spike-triggered LFP analysis indicated that firing rate encoding dACC neurons had the greatest effect on LFP in both dACC and dlPFC. Finally, spike-theta coherence in dlPFC predicted reaction time on a trial-to-trial basis, indicating a proximal relationship between neuronal activity and behavior (Figure 2).

Conclusions
The large majority of PFC neurons that do not demonstrate firing rate coding, previously assumed to be uninvolved bystanders, actually do participate in a temporal coding strategy that is both task- and behaviorally relevant. Temporal coding is emerging as a scheme used by several brain regions to facilitate communication and encode a wide dynamic range of information in a noise-robust manner. We propose that small populations of rate coding neurons (specialized "soloists") entrain oscillatory potentials to recruit a larger population of temporal coding neurons ("choir") that in turn stabilize and boost representations across the broader cognitive control network.

109 Regional Specialization in the Processing of Cognitive Conflict

Matthew Mian; Emad N. Eskandar

Introduction

Cognitive conflict occurs when processing of an irrelevant stimulus feature impairs performance of a task. Functional imaging studies have framed a model (Matsumoto et al, 2004) in which conflict is identified by the anterior cingulate cortex (ACC) and then resolved by other regions, namely the dorsolateral prefrontal cortex (DLPFC), but this hypothesis has not been validated with invasive electrophysiology.

Methods

We recruited 11 subjects undergoing stereotactic EEG for seizure focus localization to perform a standard cognitive task that introduces varying levels of conflict: the Multi-Source Interference Task (Fig 1). Depth electrodes recorded local field potentials from the ACC and DLPFC.

Results

Subjects performed the task accurately (272 ± 68 trials each, 95.3% correct), and they showed anticipated conflict-mediated response slowing ($p < 0.002$ for each subject; Fig 2). Recordings from the ACC ($n = 127$) and DLPFC ($n = 401$) revealed task-related activations in the theta and gamma frequency ranges at similar proportions of sites, with sites in both regions demonstrating sensitivity to level of conflict in each frequency band. We used Granger Prediction to assess the directionality of conflict processing, finding task-related theta band activation to be driven by the ACC rather than the DLPFC (Fig 3). Further, theta-gamma phase-amplitude coupling is greater from the ACC to DLPFC than vice versa. Finally, an inverse correlation between gamma activation and response time was observed at sites in the DLPFC but not in the ACC (Fig 4).

Conclusions

Detection of cognitive conflict is driven by the ACC, with interregional communication mediated by signaling in the theta band. Gamma oscillatory activity in the DLPFC predicts subject response times, evidencing a role for the DLPFC in the resolution of conflict. These findings lend support to the regional specialization posited in the dominant conflict monitoring model.

110 Implantation of Tissue Grafts into the Substantia Nigra to Modify Disease Progression in Parkinson's Disease: One Year Clinical Update

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Introduction

We present an ongoing open-label, Phase I trial, (NCT01833364 and NCT02369003), examining the safety and feasibility of grafting autologous peripheral nerve tissue to the substantia nigra (SN) in patients with Parkinson's disease (PD). Schwann cells are abundant within peripheral nerve tissue and transdifferentiate after nerve injury to become "repair cells" that promote regeneration. Repair cells up-regulate and release growth factors including GDNF, NGF, BDNF, and NT-3.

Methods

Our trials are open label, adaptive, and capture outcome data. Graft tissue is harvested from the sural nerve and deployed during routine deep brain stimulation (DBS) surgery. Immediately after placing electrodes into either the subthalamic nucleus (STN) or globus pallidus internus (GPi)) a section of sural nerve is excised, stripped of the epineurium, cut into 1 mm pieces, and unilaterally delivered along 5 mm of the SN. The primary endpoints are safety and feasibility. Of our secondary endpoints, the Unified Parkinson's Disease Rating Scale (UPDRS) scores are presented here.

Results

To date, 26 participants have received a single implantation to the SN. The overall adverse event profile is comparable to standard DBS surgery, with no serious adverse events related to the delivery of the graft. 22 subjects have reached the 1 year time point and demonstrated a decrease of 7.6 points in the UPDRS motor scores off medication and off stimulation (27.6 ± 12.6, mean ± SD) compared to before surgery (35.0 ± 11.7), representing a moderate clinically important difference. For comparison, 16 PD patients who received only GPi DBS showed an increase of 0.3 ± 15.0 points in their mean UPDRS motor score (off medicine and off stimulation) one year post-implant

Conclusions

The results provide evidence for safety and feasibility of delivering graft tissue with DBS and provide preliminary clinical evidence of potential baseline improvements at one year.

111 Differential Effects of Low and High Frequency Pallidal Stimulation of Pallidocortical Network in Parkinson Disease

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Introduction

Excessive beta oscillations within the brain's motor networks are well described in Parkinson disease (PD). There is evidence that therapeutic high frequency deep brain stimulation (HF-DBS) at subthalamic nucleus (STN) or globus pallidus internus (GPi), decreases basal ganglia local power in low-beta (13-20 Hz) without modulating the motor cortical power. Moreover, HF-DBS suppresses cortical phase amplitude coupling (PAC) and STN/GPi-cortical coherence at high-beta range (21-35 Hz). In this study, we contrasted the effects of non-therapeutic low frequency stimulation (LF-DBS) and HF-DBS at the GPi on pallidocortical network to further differentiate the pathophysiological role beta sub-bands in PD.

Methods

We recorded GPi local field potentials (LFP) concurrently with electrocorticography (ECoG) signals from ipsilateral sensorimotor cortices in six subjects with idiopathic PD. Recordings were acquired during DBS lead implantation surgery in the GPi while subjects were resting, off stimulation and with HF- and LF- DBS (185 and 20 Hz respectively, with random order of experiments). We assessed changes in local spectral power at the GPi and sensorimotor cortices, along with pallidocortical coherence and cortical PAC.

Results

Local GPi low beta (13-18 Hz) power was suppressed without cortical power modulation with both stimulation types ($P<0.05$, two-group test of spectra). However only HF-DBS resulted in a significant decrease in the pallidocortical coherence ($p=0.02$) and cortical PAC ($P=0.03$) within the high beta range (Wilcoxon signed-rank test). LF-DBS did not result in a significant modulation of the coherence or cortical PAC ($P>0.05$).

Conclusions

Our results lend further support on the functional dissociation between low and high beta sub-bands in motor control. Therapeutic stimulation specifically modulates high-beta coupling (coherence and PAC), highlighting its association with PD pathophysiology. In contrast, pallidal low-beta power is non-selectively modulated with both LF- and HF-DBS.

112 Significant Local Increase of GABA in STN and GPi in Response to High Frequency Stimulation (HFS): Contribution of Intraoperative Microanalysis in PD

Maria Gabriela Dos Santos Ghilardi; Raquel Martinez; Aline Auada; Ivo Lebrin; Erich Talamoni Fonoff

Introduction

DBS is a recognized treatment for PD. Despite its wide use, the precise mechanism of action and improvement of symptoms still lacks in certainty. Several mechanistic hypothesis have been raised that are probably simultaneously involved, including electrical and neurochemical changes. Experimental evidence suggest that stimulation triggers different responses depending on the neuron content, inhibiting neuronal activity locally and increasing the action potential output by activating axon and dendrites. Previous human studies have showed decreased firing rates during stimulation in GPi and STN. GABA, the major inhibitory neurotransmitter of the brain, is supposed to be involved on that once both targets receive GABAergic afferent fibers.

Methods

We performed intracerebral microdialysis in 6 consecutive patients undergoing STN-DBS and 4 consecutive patients undergoing GPi-DBS implantation. Routine stereotactic procedure was performed as the patients are part of a randomized study that compares the effect of both targets (GPi versus STN). After imaging and microelectrode mapping defined the ideal target, the dialysis probe and DBS electrode were inserted through two adjacent channels of the microdrive according to the best microrecording profile, reaching the best clinical targets in either STN or GPi. The dialysates were then collected every 10 minutes after baseline stabilization through the experiment, before, during and after HFS. We sequentially collected 3 samples for stabilization, 3 baseline samples, 01 sample during high frequency stimulation of the target and 03 samples post-stimulation. GABA concentrations were analyzed by HPLC.

Results

There was a significant increase in GABA levels in GPi by 23% and 18% ($F(1,2)=5.53$, $p=0.04$) and STN 16% and 22%($F(1,2)=5.44$, $p=0.02$) during stimulation and post-stimulation in comparison with baseline levels respectively.

Conclusions

We demonstrated, for the first time in humans, that macrostimulation increases local GABA concentrations at both GPi and STN. These findings corroborate the hypotheses that HFS activates presynaptic terminals on afferents and local interneurons in both particular targets particular targets.

113 Assessment of Rapid Fluctuations in Parkinsonian Symptoms using a Continuous Motor Assay

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Introduction

A rapid, continuous assessment of motor symptom fluctuations in Parkinson's Disease (PD) could aid the development of closed-loop interventions ranging from automated deep brain stimulator programming to fully closed-loop neuromodulation. Existing measures do not assess short-timescale symptoms. Therefore, we designed a multi-dimensional, continuous motor assay on a stylus-tablet interface and applied it to compare the performance of PD patients versus control subjects.

Methods

Fifteen PD patients and ten age-matched controls performed a target tracking task administered on the tablet. The target moved semi-randomly in a continuous path, and subjects tracked it with a pen-like stylus. Their baseline motor performance was quantified using metrics including tremor magnitude, vector error, and the Euclidean distance from the target. The data were analyzed in one-second windows across six minutes of continuous movement to generate symptom profiles. Each patient was compared to the aggregate control data using the Receiver Operating Characteristic (ROC), and the frequency of symptomatic state was classified into three categories based on the area under the curve (AUC): infrequent (< 0.6), intermediate (0.6-0.8), and frequent (0.8-1.0).

Results

Of the 45 analyses using 15 patients and 3 metrics, 44 (97.8%) were statistically significant based on the bootstrap technique ($p < 0.005$, N=2,000 replications). For tremor magnitude, the symptomatic states in patients were classified into five (33.3%) infrequent, five (33.3%) intermediate, and five (33.3%) frequent. For vector error, there were five (33.3%), seven (46.7%), and three (20.0%), respectively. For distance, three (20.0%) were intermediate and twelve (80.0%) were frequent. All PD patient metrics showed higher means compared to controls, and patient vector error and distance had broader distributions ($p < 0.001$ and $p < 0.005$, respectively).

Conclusions

PD motor behavior varies widely across patients on timescales of seconds. This motor assay captures rapid symptom fluctuations, which could serve as behavioral biomarkers for closed-loop sensing.

114 Six Year Outcome of Focused Ultrasound Thalamotomy for Essential Tremor

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Introduction

Focused ultrasound thalamotomy has been recently proposed as a treatment option for medication-refractory essential tremor. Class 1 evidence led to FDA approval in July 2016, but clinical outcomes have been typically reported at one year or less.

Methods

A pilot study of 15 ET patients, treated with unilateral FUS Vim thalamotomy, was conducted in 2011. Clinical outcomes were assessed for tremor, disabilities, quality of life, MRI, and adverse event reporting. These patients were recently assessed at six years with CRST, QUEST, and global impression of clinical change. A correlation analysis of their long term clinical outcomes was conducted including lesion volumes.

Results

Thirteen patients (87%) were assessed at 6 years post thalamotomy. One patient was lost to followup and another died from breast cancer. There was no additional, latent procedural morbidity. Mean hand tremor scores (baseline: 20.4+5.2), which were improved by 74% (5.2+4.8) at one year, remained improved by 40% (11.8+10.7) at 6 years but with some loss of effect. Seven of the thirteen patients available for followup had over 50% reduction of hand tremor at 6 years. Mean disability scores remained improved from baseline by 50% at long term. Additional outcomes including total CRST, simulated eating task, and quality of life from the QUEST are improved at long term.

Conclusions

FUS thalamotomy can provide long term benefit for ET, but tremor recurrence occurs. Further refinements and experience from this early stage study should improve the durability and reliability of FUS thalamotomy.

115 Calcium Imaging of the Nucleus Accumbens Reveals Distinct Physiological Effects of Continuous vs Responsive Neurostimulation

Hemmings Wu; Bina Kakusa; Boris D. Heifets; Daniel Christoffel; Robert C. Malenka; Casey H. Halpern

Introduction

We recently reported that responsive neurostimulation guided by nucleus accumbens (NAc) field potential ameliorates binge eating in mice. However, the mechanism remains unclear, as electrical stimulation artifact complicates signal processing. Here, we utilize, for the first time, in vivo calcium imaging, to record intracellular calcium levels as a proxy for neuronal activity during simultaneous stimulation. Specifically, we used fiber photometry to capture calcium transients in NAc neurons in awake behaving mice to directly assess the physiological differences of continuous and responsive neurostimulation. Our findings are expected to inform stimulation mechanisms not fully appreciated to date.

Methods

AAV-hSyn-GCaMP-6f virus injection, followed by optetrode (fiber optic surrounded by four platinum/iridium electrodes) implantation were performed in the NAc of mice (N=6;male C57-BL6). Mice were then put on a limited (1-hour/day) high-fat exposure protocol known to induce binge-eating behavior. Continuous and responsive neurostimulation (delivered in 10-second epochs) at different frequencies (3Hz, 10Hz, 130Hz) were administered with simultaneous calcium fluorescence imaging. The behavioral and physiological effects of different stimulation protocols were assessed.

Results

Stimulation delivered at 130Hz significantly ameliorated binge eating. Fiber photometry revealed massive increase in GCaMP fluorescence (>300%), indicative of an increase in intracellular calcium concentration. This increase in GCaMP fluorescence within the NAc lasted roughly 60 seconds with return to baseline despite continuous stimulation for an hour. Responsive stimulation (delivered intermittently) led to a consistent increase during each stimulation epoch. Three and 10Hz stimulation induced minimal change in GCaMP fluorescence with no effect on binges.

Conclusions

Imaging intracellular calcium levels during continuous and responsive neurostimulation revealed distinct physiological mechanisms, though both effectively ameliorate binge eating. This similarity suggests both stimulation protocols can disrupt the role of the NAc in mediating binge eating. Future investigation includes novel correlations across recording modalities to better define the relationship between the calcium fluctuations and neuronal activity.

116 Using DBS of the Median Forebrain Bundle to Treat Depression: Comparing Probabilistic DTI in Responders and Non-responders

Christopher R. Conner; Albert J. Fenoy

Introduction

Depression is a debilitating condition affecting millions, but despite advances in pharmacology up to 30% of patients suffer from treatment refractory depression (TRD). Deep brain stimulation (DBS) has been used as a novel therapy, with interest in white matter stimulation given the distributed nature of TRD.

Methods

In nine patients, diffusion-assisted targeting for DBS of the median forebrain bundle (MFB) was performed. A pre-operative MRI was collected, and each patient's MFB was mapped using deterministic tractography. Response to DBS was monitored using the Montgomery-Åsberg Depression Rating Scale (MADRS). Probabilistic tractography was performed retrospectively utilizing the post-implantation CT scan to determine the volume of activated tissue. Individual maps were co-registered to assess group structural connectivity and compare responders with non-responders.

Results

Eight of the patients enrolled in the study experienced improvement in depression symptoms measured by MADRS. Successful DBS treatment was associated with significantly greater structural connectivity between the stimulated contact and the frontal pole, parahippocampal gyrus/amygdala, medial frontal cortex and subcallosal gyrus. These differences were greater in the left than the right hemisphere.

Conclusions

Recent studies have demonstrated the importance of functional and structural connectivity in evaluating depression. Targeting of white matter tracts, such as the MFB, allow for influence over many regions of this network. Our results show that effective DBS of the MFB is associated with greater structural connectivity to several regions classically implicated in depression, including the medial frontal cortex, the amygdala and subcallosal cortex.

117 Quantifying the Axonal Pathways Directly Stimulated during Therapeutic Subcallosal Cingulate Deep Brain Stimulation

Bryan Howell; Helen S. Mayberg; Cameron C. McIntyre

Introduction
Deep brain stimulation (DBS) of the subcallosal cingulate (SCC) is an emerging experimental therapy for treatment-resistant depression. New developments in SCC DBS surgical targeting are focused on identifying specific axonal pathways for stimulation that are estimated from patient-specific computational models. This connectomic-based biophysical modeling has proven successful in improving the response to SCC DBS therapy; however, the DBS models used to date have been highly simplistic, limiting the precision of the pathway activation estimates.

Methods
This is the first multi-patient study to use the most detailed patient-specific foundation for DBS modeling currently available (i.e. field-cable modeling) to evaluate the axonal responses to SCC DBS. Six responder patients were used to quantify the activation of four major pathways in the SCC region: forceps minor (FM), cingulum bundle (CB), uncinate fasciculus (UF), and subcortical connections between the frontal pole and the thalamus and ventral striatum (FP-ThvSt).

Results
We used the percentage of activated axons in each pathway as regressors in a linear model to predict the patient's time to well, which was the time it took a patient to respond to DBS and maintain that response for at least four weeks. Lasso regression was used to find the most parsimonious solution that could explain the greatest variance in the output response across the patient population. FM, left CB, and right CB explained 94% of the variation in time to well. Following a permutation test, the right CB was the only regressor whose coefficient was associated with a false-positive rate of <5%. Alone, activation of the right CB could explain 84% of the variance in time to well.

Conclusions
The most likely therapeutic targets for SCC DBS are the right and left CBs, followed by FM.

118 Initial Optimization of Nucleus Accumbens Deep Brain Stimulation with Coordinated Reset for Binge Drinking

Allen L. Ho; Hemmings Wu; Bina Kakusa; Monique L. Smith; Mary Salib; William J. Giardino; Peter A. Tass; Robert C. Malenka; Casey H. Halpern

Introduction

Alcoholism affects nearly 20 million Americans, and excessive binge drinking is responsible for over 100,000 deaths in the US each year. Deep brain stimulation (DBS) of the nucleus accumbens (NAc) has been proposed as a potential therapeutic but optimization of stimulatory parameters utilizing well-validated preclinical models is an important next step. We aimed to limit stimulation-on time in the NAc utilizing coordinated reset DBS (CR-DBS), a novel, spatiotemporal paradigm that induces a long-lasting reduction of pathological synchronization with a fraction of overall current delivery. Therefore, we examined the ability of conventional DBS and CR-DBS to block binge drinking in mice.

Methods

Multipolar electrodes were implanted in the NAc of male C57BL/6J mice. Binge drinking was induced via a modified two-bottle choice version of the standard "Drinking-in-the-Dark" ethanol consumption protocol. Ethanol consumption was tracked in stimulation off and DBS (130Hz, 60us, 150uA) conditions, as well as in an initial cohort receiving CR-DBS conditions (cycle repetition rate 130Hz). DBS was administered continuously for the 4 hour binge cycle, while CRS was only administered during the first hour.

Results

Relative to sham control trials, DBS resulted in a 66% reduction in binge drinking (N=10; P=0.0002). CR-DBS was delivered for only 7.5% of the stimulation 'on' time of continuous DBS, and resulted in an 86% reduction in ethanol consumption that trended towards significance (N=4; P=0.09). Water consumption was unperturbed in both cohorts.

Conclusions

Conventional DBS is effective in reducing binge ethanol consumption in mice. Additionally, with further refinement of stimulation parameters and timing, CR-DBS may be able to achieve comparable binge drinking reduction with only a fraction of current delivery. This preclinical validation supports further study, and reveals, for the first time, the promise of CR-DBS for psychiatric conditions.

119 Induction and Quantification of Plasticity in Human Cortical Networks

Yuhao (Danny) Huang; Corey J. Keller; Jose Herrero; Maria Fini; Victor Du; Fred A. Lado; Christopher Honey; Ashesh Mehta

Introduction

How does human brain stimulation result in lasting changes in cortical excitability? Uncertainty on this question hinders the development of personalized therapies for neuropsychiatric disorders. In this study, we examined the neuroplasticity effects of repetitive stimulation by pairing direct electrical stimulation with recordings from the cortical surface.

Methods

To characterize how inter-regional networks are altered by stimulation, we applied repetitive direct electrical stimulation in eight human subjects undergoing intracranial monitoring. We evaluated single-pulse corticocortical evoked potentials (CCEPs) before and after repetitive stimulation across prefrontal, temporal and motor cortices. CCEP mapping measures causal local and remote electrophysiological responses with accurate localization of the stimulated region (1).

Results

First, we asked if a single session of repetitive stimulation was sufficient to induce excitability change across distributed cortical sites. In four patients undergoing prefrontal stimulation, we found a subset of regions at which 10Hz repetitive stimulation resulted in plasticity persisting for at least 10 minutes. These modulated regions were near the stimulated site and exhibited both potentiation and depression. Second, we asked if stimulation-induced plasticity could be modeled by the pre-stimulation connectivity profile of each subject. We found that cortical regions (i) anatomically close to the stimulated site and (ii) exhibiting high-amplitude CCEPs underwent plasticity following repetitive stimulation. Based on these results, we were able to predict where plasticity will occur on the cortex using individual subject's pre-stimulation connectivity profile. These findings generalized to stimulation sites in motor and temporal lobe in an independent dataset of four patients.

Conclusions

Repetitive stimulation induces predictable changes that outlast stimulation in regions anatomically and functionally connected to the stimulation target. These results show that baseline connectivity profile can be used to personalize therapeutic stimulation sites.

120 Magnetoencephalographic and fMRI Examination of the Effects of VC/VS DBS on Post-stroke Pain

Raghavan Gopalakrishnan; Scott F. Lempka; Richard Burgess; Kenneth B. Baker; Stephen E. Jones; Mark Lowe; Andre Machado

Introduction

Post-stroke pain syndrome (PSPS) is an intractable disorder characterized by unrelenting chronic pain and hemiparesis. While traditional analgesic approaches largely fail to provide long-term relief, integrative approaches targeting affective-cognitive spheres are promising. Recently, we demonstrated1 that deep brain stimulation (DBS) of the VC/VS, significantly improved pain affect and quality of life in PSPS patients. Here, we explore if this clinical improvement was reflected in magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) correlates that could serve as objective signatures.

Methods

We performed MEG and fMRI on 10 PSPS patients in the baseline, DBS-OFF and DBS-ON states. MEG: Visual cues evoked anticipation as patients awaited a painful (PS) or non-painful (NPS) stimulus to their non-affected or affected extremity. Whole brain event-related responses were examined. fMRI: We used a simple block paradigm. After initial preprocessing, the difference of fMRI z-map between ON-vs-OFF were generated on the MNI template in Talairach space for each patient and averaged as the final results.

Results

There were no significant difference between PS-vs-NPS before surgery or in the DBS-OFF condition, suggesting a loss of salience in the untreated pain state. DBS significantly modulated the N1 (parietal/prefrontal) component of NPS anticipation, restoring discrimination capacity (Fig-1a). DBS enhanced the anterior N1 (anterior cingulate ACC) among treatment responders, reflecting emotional regulation (Fig-1b). fMRI: Comparing DBS ON-vs-OFF, we observed (Fig-2) stronger activation of 1. medial parietal and frontal lobes on the non-affected side. 2. ACC contralateral to pain for both extremities.

Conclusions

DBS-induced changes in MEG correlates reflect treatment effects and could potentially serve as biomarkers for clinical outcomes. fMRI findings further corroborate MEG data showing modulation of behavioral and associative areas including ACC and fronto-parietal cortices. Overall, VC/VS DBS modulated the affective component of pain, as evidenced in clinical metrics, and greater involvement of associative-limbic structures during pain and pain anticipation.

121 Amygdala Structural Connectivity is Associated with Impulsivity and Nicotine Dependence

Ausaf A. Bari; Bayard Wilson; Hiro Sparks; Jean-Philippe Langevin; Nader Pouratian

Introduction

The amygdala has been shown to play a role in nicotine dependence by mediating reward and impulsivity. Here we demonstrate the structural connectivity of the amygdala to a broader brain reward network using probabilistic tractography. We hypothesized that amygdala connectivity with other reward-related structures correlates with impulsivity and nicotine dependence.

Methods

Diffusion and structural MRI was obtained from 197 randomly selected healthy subjects from the human connectome project dataset. Probabilistic tractography (using FSL) was performed between the amygdala and the brainstem, dorsolateral prefrontal cortex (DLPFC), hippocampus, insula, NAc, OFC, and rostral anterior cingulate cortex (rACC) (Figure 1). Seed masks were generated using automated segmentation (FreeSurfer software). Statistical maps of amygdala connectivity were generated. Impulsivity was determined using the area under the curve (AUC) on a temporal discounting monetary task. Tobacco dependence (low vs. high difficulty quitting) was assessed using DSM-based behavioral questionnaires.

Results

Structural connectivity of the amygdala to the specified structures was spatially segregated (Figure 2). The amygdala showed highest connectivity with the hippocampus, OFC and brainstem ($p < 0.001$) (Figure 3). There was a significant correlation between connectivity with the hippocampus, OFC, insula and rACC and impulsivity ($p < 0.001$ for hippocampus and OFC, $p < 0.05$ for insula and rACC). Higher connectivity with the hippocampus was associated with decreased impulsivity while higher connectivity with the OFC was associated with increased impulsivity (Figure 4). Subjects with greater nicotine dependence displayed significantly decreased hippocampal but increased brainstem and rACC connectivity ($p < 0.05$) (Figure 5).

Conclusions

The amygdala displays spatially segregated subregions with high connectivity with the hippocampus, OFC and brainstem. Connectivity with the hippocampus is correlated with low impulsivity and lower levels of nicotine dependence. On the other hand, connectivity with the OFC and rACC is correlated with higher impulsivity and higher nicotine dependence.

122 Human Caudate Nucleus Subdivisions in Tinnitus Modulation

Philip Perez; Sarah Wang; Susan Heath; Jennifer Henderson-Sabes; Danielle Mizuiri; Leighton Hinkley; Srikantan S. Nagarajan; Paul S. Larson; Steven W. Cheung

Introduction

Deep brain stimulation (DBS) of the caudate nucleus has been shown to modulate tinnitus perception, although the optional site of stimulation to produce modulation is not well defined. The current study seeks to identify caudate nucleus locations responsive to intraoperative direct electrical stimulation for tinnitus loudness modulation and relate those locales to functional connectivity maps between caudate nucleus subdivisions and auditory cortex.

Methods

This is a prospective cohort case series. Six awake subjects who underwent DBS electrode placement in the caudate nucleus with intraoperative stimulation as part of a Phase I clinical trial were analyzed for tinnitus modulation to acute stimulation at 20 locations. Resting-state 3T fMRI was used to compare connectivity strength between centroid locations of tinnitus loudness reducing and non-reducing caudate locales with auditory cortex in the 6 DBS trial subjects and 14 other non-DBS implanted tinnitus subjects with greater than moderate tinnitus severity.

Results

Acute tinnitus loudness reduction was observed at 5 caudate locations; 4 were positioned at the body and 1 at the head of the caudate nucleus in normalized Montreal Neurological Institute space. The remaining 15 stimulation runs at the caudate head failed to reduce tinnitus loudness. Compared to the caudate head, the body subdivision had stronger functional connectivity to the auditory cortex on fMRI ($p<0.05$).

Conclusions

Acute tinnitus loudness modulation is more readily achieved by electrical stimulation of the caudate nucleus body. Compared to the caudate head, the caudate body has stronger functional connectivity to auditory cortex. These findings in human subjects provide insight into the functional anatomy of caudate nucleus subdivisions and guidance for target selection in our basal ganglia neuromodulation approach to treat medically refractory tinnitus.

123 Functional Connectivity Changes in Failed Back Surgery Syndrome Patients After Spinal Cord Stimulation Therapy with Bursting vs. Non-Bursting Stimulation Patterns

Elsa V. Arocho-Quinones; Guangyu Chen; Andrew Nencka; Timothy N. Lynch; Shi-Jiang Li; Peter A. Pahapill

Introduction

Chronic back pain (CBP) has been associated with alterations in functional connectivity (FC) but data is limited and based on heterogeneous populations.[1-5] Based on our previous work, we hypothesize that FBSS patients have altered FC across networks involving emotion and reward/aversion functions, and that these changes may be correlated with spinal cord stimulation (SCS) outcomes.

Methods

Five, non-pregnant, adult FBSS patients with implanted SCS systems (Medtronic) were enrolled. All imaging protocols were approved by our MRI Safety committee. Anatomical and resting state (RS) fcMRIs were obtained during two separate visits. The subjects underwent off-and-on testing with non-bursting and bursting SCS at visits 1 and 2, respectively. Patient surveys were administered before and after SCS. Outcome measures focused on FC patterns, STM-index, and pain scales.

Results

FcMRI sequences were safely acquired for all patients with implanted SCS systems using 3T-MRI. Off-and-on testing of non-bursting stimulation resulted in a significant decrease of STM indices when non-bursting SCS was restored (mean STM-index 0.25 vs 0.13, $p=0.006$). No significant difference was seen in STM indices during on-and-off testing of bursting stimulation (mean STM-index 0.20 vs 0.19, $p=0.67$). The bursting pattern was preferred by 4 of 5 patients. All reported pain scores decreased during on testing. Pain catastrophizing scores (PCS) were significantly lower after switching from non-bursting to bursting pattern stimulation (mean PCS 17.6 vs 14.6, $p=0.02$).

Conclusions

Preliminary results suggest there is no correlation between the instantaneous pain scores and STM-index for patients with implanted therapeutic SCS systems which contrasts with findings from our previous study in FBSS patients after a successful SCS trial. STM indices for SCS-treated FBSS patients appeared to cluster around the normal levels seen in control non-FBSS patients. The STM-index may represent a biomarker specific to FBSS patients, which may help guide patient selection for SCS and treatment optimization.

124 Nationwide Shift from Percutaneous Rhizotomy to Microvascular Decompression for Treatment of Trigeminal and Other Cranial Nerve Neuralgia

Bornali Kundu; John David Rolston

Introduction

Cranial nerve neuralgias, including most commonly trigeminal neuralgia but also glossopharyngeal neuralgia and hemifacial spasm, are rare but significant disease entities for those affected. Here we report the trends in the use of common surgical interventions over the past decade to treat cranial nerve neuralgias.

Methods

We used the Centers for Medicare and Medicaid Services (CMS) Part B National Summary Data File, which provides data from a complete patient population, all of whom are over the age of 65 years and/or disabled. Data from 2000 to 2016 were analyzed using standard parametric statistics.

Results

Trends from 2000 to 2016 show increased use of open surgery, particularly microvascular decompression (MVD), and decreased use of percutaneous rhizotomy, including the destruction of the trigeminal nerve using balloon compression, glycerol injection, or thermal injury. Suboccipital craniectomy done for cranial nerve decompressions (including cranial nerves V, VII, and IX) increased by 33.9 cases per year so that in 2017 the number of cases was 167% of what it was 17 years earlier (95% CI 26.2, 41.7; F-statistic=87.2, $p<0.001$, ANOVA). The less commonly used subtemporal approach craniectomy to treat trigeminal neuralgia specifically increased by 1.13 cases per year to 184% of what it was 17 years earlier (95% CI 0.37, 1.89 F-statistic=10.2, $p=0.006$, ANOVA). On the other hand, the less invasive percutaneous rhizotomy procedures including glycerol and radiofrequency ablation for treatment of trigeminal neuralgia decreased by 42.9 cases per year (95% CI -56.0, -29.9; F-statistic=49, $p<0.001$, ANOVA), which is currently 64% of what it was 17 years earlier.

Conclusions

Overall, there was an increase in MVD operations and a decrease in percutaneous rhizotomy procedures. These trends may be related to improved surgical technique and outcomes related to open surgical decompression compared with the more transient treatment outcomes of percutaneous rhizotomy techniques.

125 A Pilot Study of Usage Patterns During Simultaneous Administration of Tonic and Sub-threshold Waveforms

Michael Gillogly; Julia A. Prusik; Jacquelyn MacDonnell; Julie G. Pilitsis

Introduction

Previously in spinal cord stimulation (SCS), patients used either tonic or sub-threshold programming. Technology can now enable both types of stimulation to be administered concurrently, at one or more anatomical locations. Here, we assess short-term follow-up of patients given the option of tonic stimulation alone, tonic stimulation combined with a sub-threshold program, and sub-threshold stimulation alone.

Methods

Twenty-six patients were prospectively enrolled and underwent a pre-operative battery of outcome measures including, Numeric Rating Scale score (NRS), Oswestry Disability Index (ODI), Beck's Depression Inventory (BDI), McGill Pain Questionnaire (MPQ) and Pain Catastrophizing Score (PCS). Patients received tonic, tonic with 1200Hz, tonic with microburst, microburst, or 1200Hz in a randomized order. Program preference and outcomes battery assessed at 6 weeks.

Results

18 patients have reached the six-week timepoint (Table 1). We saw significant improvement on MPQ($p=.007$), ODI($p=0.006$), BDI($p=0.012$), NRS-worst ($p<0.001$), NRS-best ($p=0.004$), NRS-average ($p<0.001$), and NRS-now ($p<0.001$). Five patients preferred tonic programs, two patients preferred tonic with HFS, three patients preferred tonic with microburst, five preferred HFS alone, and three did not have specific preferences. There was no significant difference in demographics and preferred mode of stimulation.

Conclusions

At six week follow-up, all total outcome measures showed patient improvement. There was no clear phenotype which preferred one mode of stimulation over another. Whether simultaneously administered therapy affects outcomes over time will be evaluated moving forward.

126 Long-Term Outcomes in the Management of Central Neuropathic Pain Syndromes

Michael D. Staudt; Alexander John Clark; Allan S. Gordon; Mary E. Lynch; Patricia K. Morley-Forster; Howard Nathan; Catherine Smyth; Larry W. Stitt; Cory Toth; Mark A. Ware; Dwight E. Moulin

Introduction

Central neuropathic pain syndromes are a result of central nervous system injury, most commonly related to stroke, traumatic spinal cord injury, or multiple sclerosis. These pain syndromes are much less common than peripheral etiologies, and consequently less is known regarding optimal treatment. In addition, the literature regarding long-term treatment is limited, and lacks external validity that could be applied to real-world outcomes. The objective of this study was to determine the long-term clinical effectiveness of the management of central neuropathic pain relative to peripheral neuropathic pain at tertiary pain centers.

Methods

Patients were identified for analysis from a prospective observational cohort study of patients with chronic neuropathic pain recruited from seven Canadian tertiary pain centers. Data regarding patient characteristics, analgesic use, and patient-reported outcomes were collected at baseline and 12 month follow-up for patients diagnosed with central (n=79) and peripheral (n=710) neuropathic pain. The primary outcome measure was the composite of a reduction in average pain intensity and pain interference. Secondary outcome measures included assessments of function, mood, quality of life, catastrophizing, and patient satisfaction.

Results

At 12 month follow-up, 13.5% (95% CI, 5.6-25.8) of patients with complete data sets (n=52) achieved a 30% or greater reduction in pain, whereas 38.5% (95% CI, 25.3-53.0) achieved a reduction of at least 1 point on the Pain Interference Scale. The proportion of patients achieving both these measures, and thus the primary outcome, was 9.6% (95% CI, 3.2-21.0). Patients with peripheral neuropathic pain (n=463) were more likely to achieve this primary outcome at 12 months (25.3% of patients; 95% CI, 21.4-29.5) (p=.012).

Conclusions

Patients with central neuropathic pain syndromes managed in tertiary care centers were less likely to achieve a meaningful improvement in pain and function compared to patients with peripheral neuropathic pain at 12 month follow-up.

127 Peripheral Nerve Stimulation for Complex Craniofacial Pain: Recent Single-institution Experience

Willard Stein Kasoff; Robert Wagner Bina

Introduction

Peripheral neurostimulation (PNS) for medically-refractory craniofacial pain is an emerging alternative to traditional surgical approaches, with safety and efficacy of trigeminal branch stimulation demonstrated in several retrospective series and a prospective trial currently in progress. We add our institutional experience to this relatively small body of published work.

Methods

Consecutive cases of trial and permanent placement of trigeminal branch stimulation electrodes by a single surgeon over 36 months were reviewed for indications and clinical outcomes. Outcomes were assessed by patient reports of pain reduction at last follow-up.

Results

14 patients underwent trial lead placement, with 11 patients undergoing permanent system placement. The most common diagnoses were idiopathic trigeminal neuralgia (N = 7) and trigeminal neuropathic pain (N = 5). Median follow-up was 14 months (range, 5   29 months). At last follow-up, 9 of 11 patients (82%) still had permanent systems still in place, with mean pain reduction of 84% (range, 50   100%). Implanted systems were well-tolerated with excellent cosmetic outcomes and high patient satisfaction.

Conclusions

We present a recent single-institutional series of peripheral nerve stimulation for complex craniofacial pain involving the trigeminal nerve. The procedure is safe, effective and durable over at least 1 year in the large majority of a carefully-selected patient population.

128 Radiofrequency Energy and Electrode Proximity Influences SEEG-guided RF Thermocoagulation Lesion Size

Michael D. Staudt; Jonathan P. Miller

Introduction

Radiofrequency thermocoagulation of epileptogenic foci via stereoelectroencephalography (SEEG) electrodes has been suggested as a treatment for medically intractable epilepsy, but reported outcomes have been suboptimal, possibly because lesions generated using conventional high energy radiofrequency parameters are relatively small. We describe a technique of delivering low energy across separate SEEG electrodes in order to create large confluent radiofrequency lesions, which may confer greater lesioning potential than conventional lesioning along a single electrode.

Methods

The size and configuration of radiofrequency lesions (n = 106) using different radiofrequency intensities (1.5, 3, 5, 7 or 10 W) and inter-electrode distances (5, 8, 10, 12, or 15 mm apart) was assessed in egg whites. MRI images from three patients who had undergone radiofrequency lesion creation were evaluated to determine the contribution of lesion intensity and electrode separation on lesion size. EEG, MRI, and clinical data were assessed before and after lesion creation.

Results

Both in vitro and in vivo analysis revealed that less energy paradoxically produced larger lesions, with the largest possible lesions produced when radiofrequency power was applied for long duration at 3 W compared to higher power settings ($p<0.05$). Linear separation of electrodes also contributed to lesion size, with the largest lesions produced when electrodes were separated by a linear distance of between 5 and 12 mm ($p<0.05$). Clinical lesions produced using these parameters were large and resulted in improvement in interictal and ictal activity. The size of clinical lesions was similar to that predicted by the in vitro analysis, with those produced at 3 W larger than at 7 W ($p<0.001$).

Conclusions

Radiofrequency lesions produced using low energy delivery between SEEG electrodes in close proximity can produce a large lesion. These findings might have advantages for treatment of focal epilepsy.

129 Coherence Between the Anterior Nucleus (AN) of the Thalamus and the Hippocampus Preditcs the Effect of AN-DBS in Temporal Lobe Seizures

Brigitte Piallat; Ariana Sherdil; Olivier David; Stephan Chabardes

Introduction

Even if the mechanisms by which deep brain stimulation (DBS) modifies the activity of the ictal network are mostly undefined, recent studies have suggested that the DBS of the anterior nucleus of the thalamus (ANT) can be an effective treatment for mesial temporal lobe epilepsy (MTLE), one of the most common focal epilepsy.

Methods

In a non-human primate (NHP) on demand model of MTL seizures we show that the ANT is actively involved during interictal and ictal periods through different patterns and that both HPC and ANT oscillate synchronously during seizures in the high beta-band. We investigated the effects of low (40Hz - as determined as the frequency of correlation of both structures) and high frequency (130Hz - as usually found in literature) ANT stimulation on three animals with MTLE seizures.

Results

We observed that the mean total time spent in seizure trend for an increase at 130 Hz, although, it decreased at 40 Hz as the mean number of seizure : from 5.8 ± 2.8 to 2.3 ± 1.9 ($p < 0.0001$). It turned out that the oscillation coherence between the hippocampus and the anterior nucleus of the thalamus was significantly related to the success of the low frequency stimulation: the more both structures had correlated activity, the more the anterior nucleus of thalamus stimulation was effective.

Conclusions

Our results suggest that the study of the coherence between the ANT and HPC during the seizure can be used to tune the ANT stimulation paradigm to significantly decrease seizure frequency and the time spent in seizure. Thus, the DBS paradigm could be customized for each patient for a better efficiency.

130 The Effects of Epilepsy Surgery on Deep Arousal Structure Functional Connectivity in Temporal Lobe Epilepsy

Hernan F. J. Gonzalez; Peter Konrad; Victoria Morgan; Dario J. Englot

Introduction

Temporal lobe epilepsy (TLE) is associated with widespread brain network perturbations and neurocognitive problems. We hypothesize that seizures lead to interictal dysfunction of brainstem ascending reticular activating system (ARAS) centers, which may contribute to neurocognitive deterioration. This is supported by our recent magnetic resonance imaging (MRI) studies of pre-operative patients with TLE, which showed decreased ARAS connectivity to fronto-parietal neocortical regions that is related to neuropsychological deficits. However, it is not known whether connectivity disturbances can improve in patients after epilepsy surgery.

Methods

We evaluated 15 adult TLE patients before and after (> 1 year) surgery, and 15 matched control subjects, and used resting-state functional MRI to measure functional connectivity between three ARAS structures and fronto-parietal neocortex.

Results

Compared to controls, pre-operative TLE patients demonstrated significant decreases in functional connectivity between ARAS structures and the neocortex ($p < 0.05$, ANOVA, posthoc LSD). After successful epilepsy surgery, the 10 (67%) patients who achieved seizure freedom demonstrated significant increases in connectivity between ARAS structures and the neocortex compared to pre-operative baseline ($p < 0.01$, ANOVA, posthoc LSD), with post-operative connectivity patterns resembling those in controls ($p > 0.6$, ANOVA, posthoc LSD). Certain post-operative connectivity increases were positively correlated with length of time since surgery, while others were positively correlated with pre-operative frequency of complex-partial seizures. Post-operative connectivity recovery was not seen in patients with persistent seizures.

Conclusions

Impairments in brainstem-neocortical connectivity are observed in TLE, but may recover with successful epilepsy surgery. Some post-operative connectivity patterns may increase with time after surgery, suggesting progressive recovery after achieving seizure freedom. These results are the first to demonstrate connectivity improvements after epilepsy surgery, and may lead to the identification of brainstem neuromodulation targets to address aberrant connectivity patterns and neurocognitive sequelae in this devastating disorder.

131 Modulating Hippocampal Neural States in a Non-human Primate Model of Epilepsy Using Asynchronous Distributed Multi-electrode Stimulation

Babak Mahmoudi; Annaelle Devergnas; Mark Connolly; Jocelyn Vuong; Robert E. Gross

Introduction

Neuromodulation is increasingly being investigated for the treatment for medically refractory epilepsy. We have found that asynchronous distributed multi-electrode stimulation (ADMES) of the hippocampus is more effective than macrostimulation (deep brain stimulation) in rodents (1), and is now being evaluated in a non-human primate penicillin (NHP-PCN) seizure model. In this study, we utilize a machine learning approach to characterize the spatial distribution of the effect of ADMES on hippocampal activities in the NHP-PCN model.

Methods

ADMES at 7Hz was applied via two 32-channel electrode arrays in the hippocampus for 10 trials of 2-minute intermittent ADMES and 40 minutes of SHAM stimulation. LFPs were recorded simultaneously using the same electrode array. Power spectral features for each electrode were extracted from 5s windows of LFPs after each ADMES and SHAM stimulation. This data was then used to train a classifier to determine whether the post-ADMES state was discernably different from the sham state.

Results

Cross-validation of the neural state classifier for each electrode-pair indicated that there were specific locations in the array where the ADMES induced observable changes in the hippocampal neural states. Next, we verified that this effect was not due to a difference in the seizure incidence between the two states by classifying between stimulation and sham for the ictal and inter-ictal segments independently. Isolating the effect of stimulation during ictal and inter-ictal segments we achieved AUCs of 0.66±0.08.

Conclusions

These findings suggest that ADMES maximally modulates neural activities at certain locations in the hippocampus in our NHP-PCN model. Analysis of this relationship will allow identifying controllable sub-circuits in the hippocampus. Finally, characterizing the modulated biomarkers of neural state and comparison with seizure biomarkers can be used to optimize this novel stimulation paradigm.

132 A Library of Human Electrocorticographic Data and Analyses

Kai Joshua Miller

Introduction

Electrophysiological data from implanted electrodes in humans are rare. Most recordings that have been performed are with epilepsy patients who have electrocorticographic (ECoG) electrodes implanted in the course of diagnostic localization of seizure focus prior to surgical resection. Only a small group of physician scientists have had the opportunity to work with these patients, and access to ECoG data has remained somewhat exclusive. It is recorded at only a few institutions around the country, often with different amplification setups, sampling rates, and behavioral variations (even within the same institution).

Methods

Therefore, we have compiled a set of 16 benchmark experiments, with over 200 individual datasets made with the same amplifiers, at the same settings, with the same person interacting with the subject and performing the experiment. Depending on where the electrodes were placed for clinical indication, we performed experiments known to be associated with covered brain areas. In every case, electrode positions have been registered to brain anatomy.

Results

All data, anatomic, and analysis files (MATLAB code) are in a common, intuitive file structure. Every study/task has at least 4 subjects with confirmed task-modulated signal change in at least 1 electrode. Our sampling rate and data format were kept uniform, and the anatomic localization was determined rigorously in each case. In the course of analyzing these data, a large number of novel analysis techniques were developed. We have made a publically available code base with the data, in such a way that all figures from published manuscripts describing these data could be directly reproduced. Four of the experiments have not been published.

Conclusions

These data, along with behavioral parameterizations, anatomic localizations, and brain-surface renderings are now available for download worldwide, without restriction on use (other than proper citation), at purl.stanford.edu/zk881ps0522. The set of analysis code will facilitate implementation of signal processing techniques that can be translated from this library to ECoG data recorded at institutions worldwide.

133 Ablation Dynamics of Subsequent Thermal Doses Delivered to Previously Heat-Damaged Tissue During Magnetic Resonance-guided Laser Induced Thermal Therapy

Sean Munier; Eric L. Hargreaves; Nitesh V. Patel; Shabbar F. Danish

Introduction

Intraoperative dynamics of Magnetic Resonance-guided Laser Induced Thermal Therapy (MRgLITT) has been previously characterized for ablations of naïve tissue. However, most treatment sessions require the delivery of multiple doses, and little is known about the ablation dynamics when additional doses are applied to heat-damaged tissue.

Methods

160 ablations from 61 patients across various surgical indications were examined. All ablations were performed using the Visualase MRI-Guided Laser Ablation System (Medtronic), which employs a 980-nm diffusing tip diode laser. Cases with multiple topographically overlapping doses at constant power were selected for this study. Single-dose intraoperative thermal damage was used to calculate ablation rate based on the maximum area of ablation achieved (TDEmax) and the total duration of ablation (tmax). We compared ablation rates of naïve undamaged tissue and damaged tissue exposed to subsequent thermal doses.

Results

TDEmax was significantly decreased in subsequent ablations compared to the preceding ablation (Initial ablation: 235.5 mm2; 2nd ablation; 183.5 mm2; 3rd ablation; 150.4 mm2; $P = <0.0001$). The ablation rate of subsequent thermal doses delivered to previously-damaged tissue was significantly decreased compared to the ablation rate of native tissue (Initial ablation = 2.332 mm2/s; 2nd ablation = 1.729 mm2/s; 3rd ablation = 1.450 mm2/s); $P = <0.0001$). A negative correlation was found between the degree of ablation rate reduction and percentage of overlap in a subsequent ablation with previously damaged tissue ($R = -.3353$; $P = 0.0007$).

Conclusions

Ablation of previously-ablated tissue results in a reduced ablation rate. Additionally, each successive thermal dose in a series of sequential ablations results in a decreased ablation rate relative to that of the preceding ablation. In the absence of a change in power, operators should anticipate a possible reduction in TDE when ablating partially-damaged tissue for a similar amount of time compared to the preceding ablation.

134 The Clinical Utility of Directional Deep Brain Stimulation - A Preliminary Single Center Experience

Marian Michael Bercu; Michael Pourfar; Alon Y. Mogilner

Introduction

Directional DBS leads have been used worldwide for a number of years, and have recently been approved for use in the US. Preliminary clinical data suggests that directional stimulation may result in improved clinical outcome. We present our early experience with directional lead programming.

Methods

A total of 55 directional leads (Abbott Infinity) were implanted in 34 patients to treat Parkinson's disease (n=27) or Essential tremor (n=7). Surgeries were performed by a single team in awake patients with microelectrode recording. Targets included STN (45 leads), Vim (8) and GPi (2). The mean follow up was 116 days (range 10-406 days). The systems were programmed by a neurologist with extensive expertise in DBS programming. Patients were programmed initially using the entire ring contact, and switched to segmented stimulation in cases of untoward side effects.

Results

In 38 of 55 patients, the active contacts were those with directional capability (contacts 2 and 3). Directional stimulation was found to be clinically superior to ring mode in five leads implanted in five different patients (4 STN, 1 Vim). In those patients, postoperative imaging demonstrated a lead localization radial error of <1.0 mm. In two patients (1 STN, 1 GPi), directionality did not improve stimulation-induced dyskinesias despite symmetrical lead placement and a radial error <0.5 mm from the planned target. In the remaining cases, clinical benefit was obtained without the need for directional stimulation, either via the use of the entire ring contact or via use of a non-directional contact.

Conclusions

Our preliminary experience demonstrates improved clinical outcome with directional stimulation in a relative minority of cases (13%), where directional stimulation was an option. Further controlled studies are clearly needed to elucidate the potential benefits of directional stimulation.

135 Reversible Complete Circuit Inhibition by Noninvasive Focused Ultrasound is Mediated by a Thermal Mechanism

David P. Darrow; Parker O'brien; Tom Richner; Theoden Netoff; Emad Ebbini

Introduction

Low-intensity focused ultrasound (LIFU) has been shown to evoke responses in the motor, sensory, and visual cortices. Transcranial focused ultrasound (tFUS/LIFU) can make reversible, functional lesions. A recent report highlights temperature-independent neuromodulation, suppressing 30% of a somatosensory evoked potential (SSEP). However, the mechanism of activation and reversible lesioning in the central and peripheral nervous system is not well understood. The mechanism of neuromodulation has not been elucidated, and while the role of temperature has been discounted, the sensitivity of the most common tool, MRI thermography, has coarse resolution. Through the use of high-precision dual-mode ultrasound mediated through a phased-array and arbitrary waveform generation, we investigated the mechanism of LIFU neuromodulation and characterized its effect.

Methods

Somatosensory-evoked potentials (SSEPs) were elucidated in Sprague-Dawley rats to isolate an accessible and active neural circuit. Concurrent imaging and therapy was incorporated through a dual-mode 32-channel phased ultrasound array with a 3.2 MHz carrier frequency targeting the ventral posterolateral nucleus (VPL). A 50 mW laser was used to create a thermal lesion in the VPL after stereotactic placement of a fiberoptic catheter.

Results

Ultrasound applied to the VPL contralateral to electrical stimulation completely and reversibly suppressed the SSEP. Ipsilateral application had no effect. The amplitude of tFUS was found to significantly impact the SSEP amplitude and shape, but LIFU delivered with a constant intensity (spatial-peak temporal average) reproduced a constant effect. Laser-mediated, reversible thermal lesions reproduced suppression of the first two peaks of the SSEP waveform.

Conclusions

Complete neuromodulation of a SSEP by LIFU at the thalamic relay was demonstrated in a fully anesthetized rat with lateral specificity. Using a previously unreported method of creating a thermal lesion using light, the thermal effect of ultrasound was found to be a critical component of the LIFU neural suppression.

136 Mapping of Primary Somatosensory Cortex of the Hand Area Using a High-density, Small Area Electrocorticography Grid for Closed-loop Brain Computer Interface

Daniel R. Kramer; Dominic Rodriguez; Michael F. Barbaro; Morgan Lee; Angad S. Gogia; Zachary Blumenfeld; Dom Grisafe; Charles Y. Liu; Spencer Kellis; Brian Lee

Introduction
The ideal modality for generating percepts of sensation for use in a sensorimotor brain computer interfaces (BCI) has not been determined. Here we report the feasibility of using a high-density "mini"-electrocorticography (mECoG) grid in a somatosensory BCI system.

Methods
Thirteen subjects with intractable epilepsy (age 19 to 62) underwent implantation of subdural electrodes for the purpose of seizure localization and cortical mapping. In addition to standard clinical electrodes, a high-density, mECoG grid was also placed (Adtech, 8 by 8, 2-mm contacts, spaced 3-mm apart) over the hand area of primary somatosensory cortex (S1) (8 left vs. 5 right sided implants). Following implantation, cortical mapping was performed with stimulation parameters of frequency: 50 Hz, pulse-width: 250micro-s, pulse duration: 4s, polarity: alternating, and current that ranged from 1mA to 15mA at the discretion of the epileptologist. Sensory percepts from electrical stimulation were recorded for location along with a description of the sensation. The dermatomal regions of the hand were partitioned into 48 anatomically distinct boxes. A box was included if sensation was felt anywhere within the box.

Results
Mean percentage of the hand covered was 63.9% (SD 34.4%). Redundancy, measured as electrode pairs stimulating the same box, was 1.98 electrodes per box (SD 2.16); and resolution, measured as boxes per electrode pair was 11.44 (SD 13.67) with 8.08 boxes in the digits and 3.35 in the palm. No seizures were induced from stimulation in S1 and no adverse events occurred.

Conclusions
In comparison to the small area of coverage and redundancy of a microelectrode system, or the poor resolution of a standard ECoG grid, a mECoG is likely the best modality for a somatosensory BCI system with good coverage of the hand and minimal redundancy.

137 Automated Trajectory Planning for Laser Interstitial Thermal Therapy of Mesial Temporal Lobe Epilepsy

Cristian Donos; Nitin Tandon

Introduction

Laser interstitial thermal therapy (LITT) is a minimally invasive surgical procedure that uses laser energy to target seizure foci, particularly for mesial temporal lobe epilepsy (MTLE). Patient morbidity and outcomes depend crucially on precise targeting and ablation. We seek to automate and optimize the process of laser probe trajectory planning to maximize ablation of the MTL.

Methods

The laser probe trajectories in individual patient space from 43 LITT MTLE patients, with good outcomes (Engel I or II in 84%, mean f/u 21 months) were registered to a standard space. The trajectories from patients in the upper quartile arranged by percentage of hippocampal ablation volume (using parcellated maps generated in FreeSurfer) were averaged to generate an optimal trajectory in standard space, using a non-linear deformation algorithm. An estimate of ablation volume for this optimal trajectory was then generated by averaging ablation volumes from the same patients subgroup, and then thresholding by voxels that were ablated in at least 50% of these patients. To evaluate if this trajectory could indeed improve the percentage of hippocampal ablation, we simulated this optimal trajectory in the patients from the 1st quartile of percentage of hippocampal ablation volume and compared the percentages of real and estimated hippocampal ablations.

Results

The left hemisphere optimal trajectory was obtained by averaging 7 patients (Q4) with a 79.6% mean percentage of hippocampal ablation and applied to 6 other patients (Q1). Using this optimal trajectory, the percentage of hippocampal ablation increased from 41.5% to 75.9% (t-test, $p<0.05$). Similarly, the right hemispheric trajectory increased percentage of hippocampal ablation from 50.6% to 82.1%.

Conclusions

Automated trajectory planning based on retrospective analysis of LITT cases, using this method, can optimize the percentage of hippocampal ablation volume. This automated optimal trajectory method substantially increased the zone of the MTL that could be ablated.

138 Improving Machine Learning Algorithms for Prediction of Successful Episodic Memory Encoding

Akshay Arora; Bradley Lega; Sarah Segar; Gray Umbach

Introduction

Previous studies suggest that closed-loop brain stimulation techniques may improve human memory performance (Ezzyat et al.). However, this strategy depends on classifying brain-states as favorable or unfavorable for successful encoding. We sought to compare the classification performance of two machine learning strategies-logistic regression (LR) and support vector machines (SVM). We also examined the influence of t-distributed stochastic neighbor embedding (t-SNE) dimensionality reduction and spectral coherence, a metric that estimates trial-by-trial connectivity, on classifier performance.

Methods

Our subject pool consisted of fifteen patients with refractory epilepsy implanted with a set of intracranial electrodes used to localize their seizure foci. While implanted, they participated in memory tasks (free recall), and we analyzed the EEG data corresponding to the encoding period using MATLAB. All our machine learning algorithms utilized the same time windows (0-800 ms and 800-1600 ms), frequency bands (delta [2.5-5 Hz], theta [5-9 Hz], alpha [10-16 Hz], beta [16-32 Hz], gamma [32-64 Hz], and high gamma [64-100 Hz]), and N-1 cross validation paradigm. The algorithms trained on data from five regions common to all subjects: the hippocampus, lateral temporal cortex, precuneus, posterior cingulate cortex, and temporal pole.

Results

With t-SNE applied, SVM outperformed LR (mean AUC = 0.68 vs. 0.60, $t=3.46$ ($df=14$), $p=0.0018$). Without t-SNE, SVM still outperformed LR (mean AUC = 0.63 vs. 0.59, $t=2.88$ ($df=14$), $p=0.006$). Our SVM algorithm that incorporated power coherence led to classifier improvements in some subjects, but did not perform significantly better than the t-SNE/SVM algorithm overall ($t(df) = 1.1$, $p = 0.156$).

Conclusions

The application of t-SNE and the use of SVM over LR improves classifier prediction of successful versus unsuccessful encoding. Further improving the predictive strength of our machine learning algorithms, such as by successfully incorporating trial-by-trial connectivity information, could improve the effectiveness of closed-loop stimulation techniques utilized to promote memory in patients with neurocognitive deficits.

139 RAD 1601: A Phase II Clinical Trial of Frameless, Coneless LINAC Radiosurgical Thalamotomy and Connectomic Thalamic Parcellation in Intractable Essential Tremor and Tremor-Dominant Parkinson's Disease

Evan M. Thomas; Richard Popple; John Fiveash; Victor W. Sung; Erik H. Middlebrooks; Anthony P. Nicholas; Frank Skidmore; Harrison Walker; Barton L. Guthrie; Mark S. Bolding; Markus Bredel

Introduction

Radiosurgery (SRS) has been used with successsuccessfully used to manage tremor in select patients with medically refractory tremor. Because of high doses, small target, and required precision, Gamma Knife has been the traditional platform. Our first objective was to develop and evaluate a safe, effective, and precise alternative on the linear accelerator without frame or cone. Our second objective was to couple treatment with high-resolution functional imaging of thalamic nucleithe thalamus. We present here a pre-clinical evaluation of the technique, pilot treatment, and recently-opened phase II evaluation trial.

Methods

Patients' pre-treatment tremor is evaluated with FTM score and PROMIS index. Patients are imaged on a Phillips Siemens 3T Magnetom Prisma MRI with additional optional Siemens 7T Magnetom MR imaging, to generate MPRAGE, SMS diffusion-weighted tractographicimaging, and multi-echo SMS resting-state fMRI sequences. Structural and functional connectivity measures are utilized to segment that thalamus into seven nuclear stuctures. The VIM is identified via thalamic parcellation and compared to stereotactic reference location and will be compared to the functional MRI segmentation. The scan is fused to a thin-slice CT simulation obtained with patient immobilized in a Qfix Encompass rigid thermoplastic mask. The VIM is targeted to 130Gy dmax. SRS is delivered on a Varian Edge linac with high-definition multi-leaf collimator (HDMLC) and intrafraction optical surface monitoring (OSMS) to ensure patient stationariness. Treatment is delivered in 13 flattening-filter free non-coplanar arcs with fixed-MLC position and pre-determined beam modulation (Virtual Cone), resulting in spherical dose distribution equivalent to 4mm Gamma Knife shot. Post-treatment imaging and FTM/PROMIS scores are compared to pre-treatment baselines at scheduled intervals.

Results

In the pilot treatment, a patient underwent left VIM thalamotomy as above. QA revealed treatment accuracy to 0.3mm. At 3 month follow-up, patient had experienced significant tremor improvement in right upper extremity, with new T1-enhancing lesion corresponding to isocenter position. Our IRB-approved phase II trial has begun accruing as of December 2017.

Conclusions

The authors believe functional imaging has significant potential for improved VIM targeting and tremor reduction in radiosurgical thalamotomy for select patients, and that the use of this novel approach maximizes patient comfort and treatment efficiency without compromise to accuracy.

140 Viability of Stereotactic Radiosurgery in the Treatment of Patients with Ten or More Brain Metastases: A Retrospective Chart Review

Elliot Schiff; Luke Swaszek; Jonathan P.S. Knisely; Adi Halthore; Sussan Salas; Nina Kohn; Michael Schulder

Introduction

This IRB-approved study was conducted to evaluate the efficacy of Gamma Knife radiosurgery as treatment in patients with 10 or more brain tumors. Between February 2014 and January 2016, 20 patients were treated with Gamma Knife radiosurgery for 10 or more brain metastases. The authors retrospectively analyzed the data from these patients, considering survival and tumor control as primary factors; and age, primary diagnosis, tumor location, radiation dose, KPS, and previous and subsequent treatments as secondary factors.

Methods

Brain volume treated with 8 Gy and 12 Gy was calculated to explore volume of treated tissue is a contributing factor to tumor control. MRI studies were reviewed at intervals of approximately 3 months, as were patient records on site. No patients below the age of 18 were included in this study.

Results

Of the 20 patients treated, 3 were excluded due to insufficient follow-up data. For the 17 included patients, the mean age was 58 (19-76). These patients were treated for a total of 323 tumors, with a median of 17 tumors per patient (10-34). The median survival for these patients was 12.5 months (1.3-16.9). It should be noted that patient survival was censored at the time of data collection, and the true upper limit of patient survival is higher than recorded here. The mean percent of brain volume treated was 0.9, with a median of 0.41 (0.07 3.38). A tumor was considered controlled if its volume was not larger than 20% compared to its size on the day of treatment. For each of the first three 3-month intervals, the median percent of tumor control was 97%, 96% and 100%, respectively in the patients with available data.

Conclusions

The number of tumors initially present was not found to have a significant correlation with general tumor control.

141 Stereotactic Radiosurgery After Transsphenoidal Resection of Pituitary Pathologies: Frailty as a Predisposing Factor

Anthony O. Asemota; Gary L. Gallia

Introduction

The association of frailty with outcome has been studied in many surgeries with frail patients being more likely to require additional treatment. Here, employing a national database, we retrospectively examined the impact of frailty in predicting additional stereotactic radiosurgery (SRS) treatment after transsphenoidal surgery (TSS) for resection of pituitary pathologies.

Methods

The 2001-2014 Nationwide Inpatient Sample was queried and consecutive patients with pituitary lesions who underwent TSS were identified using ICD-9-CM codes. Patients who also underwent SRS after TSS were also identified using the appropriate procedural codes. The odds-ratios of undergoing SRS after TSS were examined in matched propensity score analysis adjusted for multiple confounders.

Results

In total, 115,317 patients who underwent TSS resection of pituitary lesions were included. The mean age of patients undergoing TSS was 51.98 years (SD=15.91). Frailty was present in 1.73%. Frail patients were more likely to be >/=65 years (38.50% vs. 24.02%, $p<0.001$), black ($p<0.001$), possess Medicare/Medicaid insurance ($p<0.001$), of lower median income groups ($p<0.001$), and have higher comorbidity ($p<0.001$). Overall, 1.08% of patients who underwent TSS also underwent SRS procedures. The mean age of patients undergoing SRS was 54.36 years (SD15.56), mostly treated in urban centered teaching hospitals (86.97%), large bed-size hospitals (80.01%), and located in the South (31.57%) and Midwest (28.22%) regions. Results of propensity-matched and adjusted multivariate regression revealed an increased likelihood of SRS after TSS among frail patients (OR=2.60 95%CI=1.38-4.89, $p<0.001$). Patients treated in the Midwest also demonstrated increased odds of SRS (OR=1.61; 95%CI=1.11-2.34, $p< 0.001$). There was no significant independent association between patient age ($p=0.34$), or higher comorbidity ($p=0.07$) and likelihood of SRS.

Conclusions

Frailty in patients undergoing TSS predicts a greater likelihood of additional SRS treatment. These findings warrant further validation in prospective cohorts.

142 Strategies to Optimize SRS Plans for Brain Metastasis with VMAT (RapidArc)

David Wang; Harry Hu; Peter D. LeRoux; Albert DeNittis

Introduction

Prescription practice for brain metastasis in different modalities, such as Gamma Knife, Cyberknife and LINAC differs significantly and prescribed isodose line may vary up to 40%. In this retrospective study we examined strategies to optimize SRS plans (Eclipse V11) for brain metastasis with FFF VMAT including optimal prescription practice.

Methods

Forty cases were stratified by maximum target size (20 cases > 2cm and 20 <2cm) in two groups and first optimized using traditional LINAC MLC-based approaches, i.e. more uniform dose distribution in the target and prescribed to average (91.8±0.9)% isodose line of the maximum dose. The plans were compared with those optimized using new strategies, i.e. the prescribed isodose line was an average (75.3±0.7)% of the maximum dose and multi-ring structures were implemented within the target and beyond for optimization. The plan quality was analyzed by the Paddick comformity index (PCI); R50%; V12, the normal tissue volume within 12 Gy; Homogeneity Index (HI), and the Focal Index (FI)*, an indicator how much dose is concentrated in the target core. The confidence limits for all the data is the 95% confidence interval (CI).

Results

The average PCI was increased by (6.9±2.1)% with the new optimization strategies. The average R50% was decreased by (21.6±6.2)% and (26.5±4.1)%, the average V12 by (32.6±7.4)% and (30.8±5.2)% for maximum target size > 2cm and < 2cm, respectively. The average HI was increased by (22±2.3)% while the FI was increased by (43.8±4.2)%. The dose distribution in the target also was changed from concave to convex with the new optimization strategies.

Conclusions

The new optimization strategies for SRS brain metastasis with FFF-VMAT consistently create more conformal plans in both high and intermediate dose region. This results in increasing the dose in the target core while decreasing the intermediate dose to normal tissue.

143 Outcome in Patients Undergoing Stereotactic Radiosurgery: Frailty is Associated with Worse Short-term Outcomes

Anthony O. Asemota; Gary L. Gallia

Introduction

Frailty assessment is a burgeoning area of interest and its usefulness for predicting outcomes has been examined for major surgical procedures. However its impact on outcome of patients undergoing stereotactic radiosurgery (SRS) has not yet been evaluated. Employing a national database, we sought to examine the impact of frailty on outcome of patients undergoing SRS.

Methods

All patients who underwent inpatient procedures of SRS were identified from the Nationwide Inpatient Sample database 2001-2010 using ICD-9-CM codes. Frailty assessment employed the validated Johns Hopkins Adjusted Clinical Groups indicator. Standard descriptive techniques and matched propensity score analyses adjusted for multiple confounders examined outcomes.

Results

Among 37,973 cases, frailty was present in 3.08%. The mean age for frail versus non-frail patients was 60.02 years (SD±18.39) vs. 56.63 years (SD±18.05), ($p<0.001$). Frail patients were more likely to possess Medicare/Medicaid insurance ($p<0.001$), lower median income ($p<0.001$), and have higher comorbidity ($p<0.001$). Most SRS procedures occurred at teaching hospitals (85.39%), large bed-size hospitals (72.94%), in urban areas (96.50%), and in the North-east (39.07%). The commonest indication for SRS was secondary brain metastases (33.35%), and the commonest SRS modality utilized was multi-source photon (gamma knife) in 53.28%. Overall mortality was 0.82%. Frail patients demonstrated significantly higher mortality (3.10% vs. 0.75%, $p<0.001$) and were more likely for non-routine discharges (61.95% vs. 23.84%, $p<0.001$). There was a higher incidence of neurologic complications among frail patients (3.30% vs. 1.04%, $p<0.001$). The mean total charge associated with SRS was $54,942.24 (95%CI=$53,673.48-56,210.99), and was significantly higher among frail patients [$109,015.70 (95%CI=$92,905.60-125,125.90) vs. $53,208.27 (95%CI=$52,024.47-54,392.07), $p<0.001$]. Total length of hospitalization was significantly prolonged among frail patients [14.06 days (95%CI=12.12-16.00) vs. 4.16 days (95%CI=4.02-4.31), $p<0.001$].

Conclusions

Frailty is associated with worse short-term outcomes among inpatients undergoing SRS. Additional studies to more fully understand the particular role and benefits of frailty in pre-operative risk-stratification and assessment are needed.

144 Adjuvant and Neoadjuvant Radiosurgery of Two Supratentorial Intracranial Metastases in an Individual Patient with Differing Clinical and Radiographic Response: Case Report and Clinical Implications

Rachel M. Pruitt; Jonathan P.S. Knisely; David Weintraub

Introduction

Treatment of metastatic brain tumors often consists of resection followed by stereotactic radiosurgery (SRS). Recently, neoadjuvant radiosurgery has been proposed to prevent tumor recurrence and improve outcomes.

Methods

We present a case of a 48 year old man with lung squamous cell carcinoma, treated with a pneumonectomy, radiotherapy, chemotherapy, and recently started on nivolumab for refractory disease, who presented with confusion and right sided weakness. An MRI revealed a 2.3 X 2.8 cm left frontal lesion with significant edema, and a 0.7X1cm left parietal lesion. The frontal lesion was resected with clinical improvement. 28 days later he underwent SRS with 12Gy to both the resection cavity and parietal lesion, which had demonstrated asymptomatic increased size and associated edema. The day after SRS he experienced worsening right sided weakness, with worsening edema surrounding the parietal lesion. Symptoms did not improve with steroids, and the parietal lesion was resected 6 days later.

Results

A 2-month follow up MRI demonstrated recurrence within the frontal surgical bed with no evidence of recurrence of the parietal metastasis. Twenty days later he underwent an additional SRS treatment to the frontal recurrence (20Gy). A one month follow up MRI demonstrated a good response. While his neurologic disease remained stable, he eventually died of systemic disease progression.

Conclusions

In this patient with two supratentorial metastases, one treated with resection and adjuvant SRS and the other treated with neoadjuvant SRS followed by resection, neoadjuvant radiosurgery was more effective in controlling tumor recurrence. This case has clinical implications for the treatment of solitary and symptomatic brain metastases and may demonstrate some complications that can ensue from SRS to intracranial tumors in patients receiving immune checkpoint inhibitors.

Poster Presentations

501 Identifying Neuromodulation Targets for Disorders of Consciousness with Single-Pulse Electrical Stimulation

Sima Mofakham; Adam Fry; Susan M. Fiore; Charles B. Mikell

Introduction

Consciousness has been linked to functional connectivity across broad cortical networks that enable rapid integration of information across distant areas. Thus, potential targets for neuromodulation should have broad projections throughout the cortex. Here, we used single-pulse stimulation of two potential targets, prefrontal cortex and anterior cingulate cortex, to probe the connectivity of relevant cortical networks.

Methods

We enrolled four comatose traumatic brain injury patients with GCS < 8 and with no major brain structural abnormalities. After informed consent by a legally authorized representative, we implanted a stereotactic 10-contact depth electrode spanning anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC), used clinically for seizure monitoring. To probe frontal connectivity, we administered repetitive single-pulse stimulation to ACC and DLPFC (200 µS, 1 Hz stimulation, 100 reps). We recorded evoked potentials on the depth electrode, as well as on scalp contacts. Evoked responses were compared to consciousness, as measured using the Coma Recovery Scale-Revised.

Results

Both ACC and DLPFC stimulation caused broad evoked potentials, but ACC stimulation lead to bihemispheric responses. The spatial extent and amplitude of the evoked response were correlated with level of consciousness. Different patterns of activation were observed with PFC and ACC stimulation, with ACC showing a broader response.

Conclusions

ACC stimulation lead to broad evoked potentials, which correlated with the level of consciousness, a finding which was less clearly seen with PFC stimulation. This suggests that ACC could be a potential neuromodulation target for disorders of consciousness.

502 Neural Correlates of Effective DBS for Essential Tremor

Andrew Haddoc; Howard Chizeck; Andrew Lin Ko

Introduction
Despite the clinical efficacy of thalamic deep brain stimulation (DBS) for essential tremor (ET), little is known about how therapeutic DBS alters neural activity to disrupt pathological tremor. Prior studies have investigated motor cortical activity during DBS and suggest that therapeutic DBS activates cortex at the stimulation frequency or its subharmonics and significantly reduces alpha band activity (8-13 Hz), but these findings have not been confirmed in chronically implanted patients. Neural biomarkers of effective DBS may elucidate ET mechanisms and provide an alternative method by which DBS can be programmed.

Methods
We recruited two ET patients chronically implanted with VIM DBS and ECoG strip over the arm area of motor cortex. We tested a range of bipolar stimulation contacts and amplitudes at nominal frequency and pulsewidth while evaluating tremor and recording local field potentials (LFPs) from motor cortex. A smartwatch with inertial measurement unit (IMU) was used to quantify tremor and distinguish between effective (greater than 90% of tremor reduction) and ineffective DBS settings.

Results
We compared the LFP signal power in theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and subharmonic (70 Hz) bands for effective, ineffective and off DBS settings. We found that effective DBS significantly decreased motor cortical theta, alpha, and beta power relative to ineffective DBS ($p < 0.01$, $p < 0.01$, $p < 0.001$, respectively) and off DBS ($p < 0.01$, $p < 0.001$, $p < 0.001$, respectively), and that effective DBS significantly increased subharmonic power relative to ineffective DBS ($p < 0.01$) and off DBS ($p < 0.01$).

Conclusions
These findings in chronically implanted patients support previous studies that used EEG and ECoG during surgery to characterize motor cortical activity during DBS. Future studies will test additional patients and investigate whether these neural biomarkers may be used to guide DBS programming sessions.

503 Phosphene Thresholds for V1 Stimulation Reflect the Strength-duration Curve of Neuronal Excitation

Soroush Niketeghad; Abirami Muralidharan; Uday Patel; Jessy Dorn; Robert Greenberg; Nader Pouratian

Introduction

Studying the mechanism of eliciting subjective visual sensations called "phosphenes" is one way to understand the neural correlates of visual perception. Non-invasive measurements of cortical excitability during transcranial magnetic stimulation (TMS) of human primary visual cortex suggest the involvement of V1 excitation in producing phosphenes. However, electrophysiological mechanism of phosphene perception is poorly characterized by these non-invasive methods. We propose that phosphene thresholds obtained by invasive cortical stimulation of V1 provide a more reliable representation of V1 excitation and may inherit the basic characteristics of neuronal excitation, specifically the strength-duration curve.

Methods

Two parallel cortical strip leads (each with 4 contacts) was implanted over the right medial occipital lobe of a blind volunteer to assess the feasibility of a visual cortical prosthesis. Phosphene thresholds in the form of stimulation current was measured for a range of stimulation pulse-widths and frequencies in multiple time points after implantation. Current thresholds were plotted against the stimulation Pulse-widths and frequencies.

Results

Current-pulse width and current-frequency curves share the two basic characteristics of the strength-duration curve of neuronal excitation: i) a rheobase current (the minimal amplitude of infinite pulse width) is present in both curves and ii) for the lowest amount of pulse-width or frequency, a minimum charge is required to elicit a phosphene and the extra charge increases linearly as pulse-width or frequency increase.

Conclusions

The similar attributes of phosphene threshold curves and strength-duration curve of neuronal excitation suggests that V1 may be directly involved in phosphene perception. Therefore our current knowledge of neuronal excitation can be employed to generate visual perception especially in the case of visual cortical prostheses.

504 Neural Stimulation to Enhance Motor Plasticity

Xiaoyu Peng; Jordan Hickman; Dane Donegan; Cristin Welle

Introduction

Preclinical and preliminary clinical investigations have demonstrated the basic efficacy of vagal nerve stimulation (VNS) to increase cortical plasticity, and suggested a role in stroke rehabilitation. To harness the full potential of VNS to drive modification of neural circuits, more needs to be known regarding the mechanisms by which VNS drives neuroplasticity and the conditions by which it can facilitate learning.

Methods

The goal of this work is to understand the influence of temporally-precise VNS on cortical plasticity in the motor system and on the subsequent learning of a skilled motor task in healthy rodents. Mice are trained to perform a dexterous reach through a narrow slit to grab a food pellet. VNS is applied following a reach success. To test if cholinergic neuromodulation from basal forebrain (BF) afferent projection neurons may mediate this effect, we applied optogenetic stimulation to cholinergic BF neurons.

Results

Temporally-paired stimulation of the vagus nerve doubled the reach success rate on training days 2 and 3, as compared to unimplanted control animals. Stimulation of cholinergic afferent projections likewise enhanced both early and late phases of motor learning and subsequent final performance level.

Conclusions

We find that VNS stimulation and optogenetic modulation of cholinergic afferents enhance motor learning and behavior. Future work will explore circuit mechanisms for this effect, and the way in which neuromodulation shapes the plasticity of neural ensembles in motor cortex.

505 Comparing the Bitrate Communication Performance of a Wired vs. Wireless Intracortical Brain Computer Interface in a Person with Tetraplegia

David M. Brandman; Jad Saab; Thomas Hosman; Brian Franco; Jessica Kelemen; Arto V. Nurmikko; David A. Borton; Leigh R. Hochberg; John D. Simeral

Introduction

Intracortical Brain Computer Interfaces (BCIs) can enable individuals with tetraplegia to communicate and control external devices, such as computer cursors to enable point-and-click typing for communication. Current iBCIs being evaluated for human use typically rely on a tethered connection between a percutaneous pedestal and signal processing equipment enabling real-time neural decoding algorithms. Recently, the use of a full-spectrum wireless transmitter for electrophysiological recordings has been described in non-human primates, which can be used to transmit the broadband neural data to nearby receivers (Yin et. al. 2014). We sought to quantify the neural cursor control achieved by a person using this new wireless device compared to the current wired system.

Methods

Participant T10 (35 year-old man with C4-AIS Grade A spinal cord injury) was enrolled in the ongoing BrainGate2 clinical trial. For each research session (Trial Days 355 and 361), T10 completed calibration and assessment blocks as we alternated between the wireless and wired devices. We began by calibrating the neural decoding algorithms using the Radial-8 task for 3 minutes (Brandman et. al., 2018). T10 then acquired targets in a Grid Task (6x6 grid) which was used to compute the communication bit rate (Pandarinath et. al. 2017). 14 Wired and 10 wireless grid task blocks (2 minutes each) spanning the two days were evaluated.

Results

There was no statistically significant difference in the communication bit-rate between the wired and wireless devices (N = 587 targets, median 1.49 bits/s vs. N = 399 targets, median 1.55 bits/s, Wilcoxon-rank sum test p=.46).

Conclusions

These results show the viability of a broadband wireless transmitter for iBCI-enabled point-and-click communication, enhancing the potential for iBCI systems to improve the functional independence for individuals living with paralysis.

506 Evaluation of Thermal Changes Needed for Focused Ultrasound Modulation of Neuropathic Pain

Abigail Hellman; Teresa Maietta; Goutam Ghoshal; Paul Neubauer; Clif Burdette; Julie G. Pilitsis

Introduction

Thermal ablation modalities for neurosurgical use currently include laser interstitial thermal therapy and transcranial MR guided focused ultrasound. There is mounting evidence that focused ultrasound (FUS) can also be used to modulate rather than ablate nervous tissue. In contrast to ablative lesions, which tend to require temperatures of above 60°C, the thermal changes needed for neural modulation have not been defined. Currently, MR thermal imaging lacks the sensitivity to measure the subtle temperature changes required for neuromodulation. In this preclinical study, we demonstrate the feasibility of using a thermode to evaluate temperatures associated with FUS neuromodulation.

Methods

Seven-week-old male Sprague-Dawley rats were treated with vincristine (intraperitoneal injection of .01mg/kg) to induce chemotherapy induced neuropathic pain. FUS was applied to the left L5 dorsal root ganglia (DRG) guided by a thermode at the area. Responses of the left hindpaw to Vonfrey filament and the Randall Selitto test (RST) to evaluate innocuous and noxious mechanical stimuli respectively, were evaluated before and after FUS treatment.

Results

The mean rise in temperature was 3.2°C from a baseline of 32.4°C ± 0.21°C to 35.6°C ± 0.12°C. This 3°C temperature change resulted in decreased sensitivity of mechanical thresholds from baseline through day 5 ($p=.019$). RST also demonstrated significant differences post treatment ($p=.032$). A power amplitude of 2.5W for a duration of 3 min achieved these goals.

Conclusions

Here we demonstrate that a 3°C change in the DRG during FUS can modulate behavioral effects for 5 days post treatment. Our ablative work suggests that nervous tissue is more susceptible to thermal changes than muscle or liver due to its acoustic properties. Moving forward we will develop an external thermode to be used on our FUS delivery device that resembles a diagnostic ultrasound to offer a fully external option for treatment of pain.

507 Real Time Confirmation of Subthalamic Deep Brain Stimulation Lead Location by Comparison of Microelectrode Recordings and Local Field Potentials From the Implanted Lead

Salam Oukal; Hagai Bergman; Zvi Israel

Introduction

Microelectrode recording (MER) during deep brain stimulation (DBS) surgery targeting the Subthalamic nucleus (STN) is a useful tool to help confirm the target. The subsequent manual insertion of the permanent lead in the MER track may be associated with error, and many centers use fluoroscopy to verify lead location. Here we describe a technique utilizing physiological data to confirm lead location.

Methods

Data was collected from 23 patients who underwent STN DBS for Parkinsons disease. 20 patients were implanted with the Medtronic 3389 lead and 3 patients with the Boston Scientific DB 2202 lead. Leads were implanted in the optimal position as defined by MER. Local field potentials (LFPs) were recorded from all contacts simultaneously. The spike (SPK - absolute of the 300-6000Hz band-passed data) and LFP (1-70 Hz band-passed) data collected from the lead recordings were analyzed and compared to the SPK and LFP from the microelectrode contacts, as well with the SPK and LFP of the macroelectrode contact, positioned 3mm above the microelectrode.

Results

Primary analysis reveals correlation between MER recordings and recordings from DBS Lead as well as high accuracy of detecting the beta oscillations in the Dorsal Lateral Oscillatory region of the STN in compare to the Microelectrode recording beta detection. Additionally we succeeded to show directional detection using Boston scientific segmented Lead in compare to multiple MER tracks.

Conclusions

Recording from the implanted DBS lead can confirm lead location based on the electrophysiological signature of the STN target.

508 Electrocorticographic Changes in Alpha, Beta, and Gamma Band Power Following Tactile Sensation in Humans

Daniel R. Kramer; Michael F. Barbaro; Angad S. Gogia; Zack Blumenfeld; Morgan Lee; Kelsi Chesney; Dom Grisafe; Charles Y. Liu; Spencer Kellis; Brian Lee

Introduction

We sought to understand the neurophysiological response properties of neurons in the hand area of primary somatosensory cortex (S1) via ECoG during mechanical touch of the subject's hand.

Methods

Two patients with epilepsy were implanted with subdural ECoG grids over S1 in the hand area. These patients had either a "mini"-ECoG grid consisting of 64, 2-mm contacts, spaced 3-mm apart (21 F, left sided implant) or a "standard"-ECoG grid consisting of 20, 5-mm contacts, spaced 10-mm apart (25 M, right sided implant). A region on the hand that correlated to the contralateral cortex covered by the grid was subject to 15 trials each of three types of mechanical touch: soft touch (cotton gauze lightly brushed repetitively), light touch with a tongue depressor (no indentation of the skin), and deep touch with a tongue depressor (indentation of the skin). Local field potential from these trials was then analyzed off-line. Power was calculated and normalized, and then evaluated for significance using a permutation test (N=10,000).

Results

All three types of touch showed significant decreases in power in the alpha (8-12 Hz) and beta (12-40 Hz) bands immediately following the onset of touch and returning to baseline around 400ms after onset in the electrode pair associated with the dermatomal region. The spread of gamma band activity (40-170 Hz) showed a significant increase in power centered around 300ms after touch onset and extinguishing around 600ms. All changes happen earlier in deep touch than light or soft touch. The decrease in alpha and beta power was found in the electrodes surrounding the primary two electrodes extended throughout the grid.

Conclusions

Decreases in alpha and beta band power were associated with touch onset as well as an increase in gamma power centered over the area of S1 associated with the area of touch; similar to prior work.

509 A Dental Fixation of Fiducials Can Improve the Accuracy of the Frameless Stereotaxy

Andrey I. Kholyavin; Vladimir B. Nizkovolos; Juri Z. Polonsky

Introduction

The accuracy of existing frameless neuronavigation systems and the possibility of their use for stereotactic guidance largely depend on the method of registration. It is known that the highest accuracy is provided with registration using bone-implanted fiducials, but the disadvantage of this method is the invasiveness.

Methods

Alternative option for bone fixation of fiducials is detachable fixing of markers to the teeth of the upper jaw of a patient using the dental impression. This method provides a rigid immobility of the markers relative to the skull and the reproducibility of their spatial position during repeated biting of dental impression. As the support for fiducials we use device consisting of an aluminum arc and four rods with standard toroidal markers for CT and MRI. During a preoperative scanning and further surgery at the time of registration this device is reproducibly fixed to the patient's head with individual tooth impression. For navigation we use Medtronic StealthStation S7, supplemented with neurosurgical manipulator of stereotactic system POANIC, allowing for mutually perpendicular movements of a stereotactic instrument. For targeting we use the function virtual extensing of the instrument provided by the navigation station.

Results

We performed a series of phantom tests using this methodology. Results showed an average targeting error of 0.87 ± 0.33 mm for CT and 0.91 ± 0.56 mm for MRI-guidance. In clinical practice, this method has been engaged by us when performing operations in 10 patients with bilateral DBS of STN and GPI, 5 patients with stereoEEG and 19 patients with biopsy and stereotactic cryoablation of deep-seated gliomas. In patients with implanted electrodes, the average error of implantation was 1.66 ± 0.72 mm.

Conclusions

The introduced method allows to achieve accuracy corresponding to the use of bone-implanted markers, but it is less invasive and provides more comfortable conditions of frameless stereotactic procedure for patients.

510 Identification of Electrode Locations Within Hippocampal Substructures Using Ultra-High Field Magnetic Resonance Imaging

Jonathan C. Lau; Jordan DeKraker; Keith MacDougall; Holger Joswig; Andrew G. Parrent; Jorge Burneo; David A. Steven; Terry M. Peters; Ali R. Khan

Introduction

The hippocampus is commonly implicated in drug-resistant epilepsy with characteristic involvement of specific sectors of the cornu ammonis (CA) [1]. It can be divided longitudinally into the head, body, and tail; and unfolded along the medial-to-lateral axis into specific subfields: the subiculum, CA sectors, and dentate gyrus. The increased signal at ultra-high magnetic field strengths (= 7 Tesla; 7T) allows these substructures to be visualized in continuity at submillimeter resolution. We propose to use 7T magnetic resonance imaging (MRI) to identify intracerebral electrode locations within hippocampal substructures.

Methods

53 patients with drug-resistant epilepsy were identified undergoing first-time electrode implantation. Post-operative computed tomography scans were registered with the pre-operative MRI permitting localization of the electrodes in MRI space. Electrode contacts within the hippocampus were semi-automatically labeled [2]. Each patient MRI scan was subsequently aligned with a recently developed 7T template space (0.6 mm isotropic voxel size) [3]. Transformation of electrode locations into our recently developed unfolded coordinate space [4] permitted labelling of hippocampal substructures (Figure 1).

Results

Bilateral electrode contacts were superimposed onto the unfolded coordinate space (Figure 2). Out of a total of 178 implanted hippocampal electrodes (88 left; 49.4%), 25 (14.0%) were predominantly in the subiculum, 85 (47.8%) were in CA1, 23 (12.9%) were in CA2, 18 (10.1%) were in CA3/CA4, and 27 (15.2%) were in the dentate gyrus. Along the longitudinal axis of the hippocampus, electrodes were most commonly implanted in the body (92; 51.7%) followed by the head (86; 48.3%).

Conclusions

Here, we demonstrate the use of 7T MRI to assist with identifying the location of electrode implantations within hippocampal substructures. While limitations with existing electrode technology may prevent our ability to observe electrographic differences based on location, our findings suggest that at least from an imaging perspective, specific targeting of hippocampal substructures is feasible using ultra-high field MRI.

511 Hippocampal Volume Changes Following Anterior Thalamic DBS for Epilepsy

Darrin J. Lee; Gavin Elias; Andres M. Lozano

Introduction

Anterior thalamic nucleus deep brain stimulation (ATN DBS) has been shown to decrease seizure frequency in drug-resistant epilepsy, although the underlying mechanism for seizure reduction is not entirely understood. Prior studies suggest that surgical resection of mesial temporal sclerosis results in decreased hippocampal volumes on the contralateral side. Here, we evaluate hippocampal volumetric changes following ATN DBS and correlate these with seizure outcome.

Methods

Five patients (2 female, 3 male; mean age 30.8±12.8 years) underwent bilateral ATN DBS for medically refractory epilepsy, while 22 patients (11 female, 11 male; mean age 37.8±10.7 years) underwent surgical resection for mesial temporal sclerosis. Serial T1-weighted brain MRIs were acquired before and after surgery for each cohort (average of 5.3±1.7 years after ATN DBS, 1.0±0.5 years after surgical resection). Blinded, manual hippocampal segmentation and volumetric analysis was performed.

Results

Consistent with previous findings, there was a reduction in hippocampal volume contralateral to the resected hippocampus in the surgical resection cohort (preop: 2879±319mm3 vs. postop: 2756±326mm3, $p<0.01$). In the ATN DBS cohort, there was no difference between preoperative (3516±782mm3) and postoperative hippocampal volume (3553±1056mm3; $p=0.80$). However, three of five patients exhibited an increase in right and left hippocampal volumes following continuous thalamic DBS. In the two patients who demonstrated significant seizure reductions ('responder group'), the hippocampal volume increased (6.6±9.0%); however, the hippocampal volume did not significantly differ from that of non-responders (-5.3±14.2% decrease). The responder group had significantly larger preoperative (responder: 4165±530.5mm3 versus non-responder: 3084±609mm3, $p<0.05$) and postoperative (responders: 4416±310mm3 versus non-responders: 2978±978mm3, $p<0.05$) hippocampal volumes compared to non-responders.

Conclusions

Preoperative hippocampal volume might predict responsiveness to ATN DBS and guide prognosis. Further studies are necessary to determine if efficacious ATN DBS results in stable or increased hippocampal volumes and whether volume changes relate to ATN DBS' mechanism of seizure reduction.

512 Functional Connectome-based Biomarkers of Epileptogenesis in Drug-Resistant Human Epilepsy

Farid Hamzei-Sichani; Stefan Fuertinger; Kristina Simonyan

Introduction

About one third of epilepsy patients do not respond to medical treatment, but can still benefit from surgical treatment. Despite recent technological advances in epilepsy surgery, 30%-50% of patients with drug-resistant epilepsy never achieve seizure freedom. This is due, in part, to the lack of objective methods for identification of the epileptogenic brain areas prior to surgical intervention. Several lines of evidence have shown that pathological high frequency oscillations (HFOs) at 100-500 Hz recorded via intracranial EEG are involved in epileptogenesis. However, to date there is no reliable approach to detect and classify pathological from normal HFOs for proper identification of epileptogenic activity.

Methods

We used a graph theoretical analysis of intracranial EEG recordings (subdural grids) in patients with drug-resistant epilepsy in order to identify pathological HFO network activity patterns. The high frequency oscillations were classified into ripple (80-250 Hz), fast ripple (250-500 Hz) and HFO (100-500 Hz) bands. Functional connectivity as mutual information of intracranial EEG signals recorded at each electrode, were quantified and normalized for each pair of electrode time series.

Results

We found that during no-seizure states, cortical networks at all high frequency bands were characterized by stable network structure (modular structure) measured by the average number of nodal communities. Iirregular partitioning of the network architecture led to an increased average number of nodal communities during the pre-ictal period in all high-frequency bands (corrected $p = 0.03$). This "modular breakdown" was seen on average 3-4 minutes before the electrographic seizure onset.

Conclusions

Functional connectome-based measures of HFO dynamics in contrast to single-channel pathologic HFOs have a high potential in facilitating the development of novel biomarkers for epileptogenesis.

513 A Protocol for Withholding Prophylactic Antiepileptic Drugs in Seizure Naive Patients Undergoing Craniotomy for Tumor Resection

Madison Remick; Deborah A. Cushing; Anand Rughani; Jeffrey Florman

Introduction

The use of prophylactic antiepileptic drugs (AEDs) in patients undergoing craniotomy for tumor resection is controversial. Published studies suggest that prophylactic administration of AEDs is unnecessary, especially in patients who are seizure free at the time of craniotomy. Based upon this literature, we hypothesized that cessation of prophylactic AEDs in patients undergoing craniotomy does not result in a significant increase in seizures. Our neurosurgical team implemented a protocol for withholding AEDs in seizure naive patents at the time of craniotomy for tumor resection.

Methods

A chart review was performed in which we identified all patients undergoing craniotomy for tumor resection. From this cohort, we identified those from whom AEDs were prospectively withheld as well as those who were seizure free at the time of surgery. Patient data such as age, gender, tissue diagnosis, and seizure history were collected over a period from January 2013 through June 2017. The seizure incidence rates between individuals who did not receive prophylaxis were compared to matched controls who received AED therapy.

Results

A total of 743 eligible patients were identified. After an initial chart review, 629 (317 female) underwent craniotomy for tumor resection. Of this cohort, a total of 397 (63%) patients had no prior history of seizure(s) at the time of tumor resection; of which 217 (55%) did not receive prophylactic AEDs. Of the seizure naive patients who did not receive AED prophylaxis, 7 (3.2%) experienced a postoperative seizure in comparison to 6 (3.3%) patients who were given prophylactic AEDs ($p=0.58$; Fisher exact test).

Conclusions

From this dataset we observed no statistically significant difference in the incidence of new post-operative seizure(s) following implementation of our protocol when compared to controls who received AED therapy. This preliminary observation is intriguing and warrants further study in order to more accurately define the therapeutic index of prophylactic AED therapy.

514 The Association of Hospital Volume and Outcome in Patients Undergoing Deep Brain Stimulation

Anthony O. Asemota; Gary L. Gallia

Introduction

The association of surgical volume and outcome has been examined for most neurosurgical procedures. We sought to investigate the volume-outcome relationship among inpatients undergoing deep brain stimulation (DBS) procedures.

Methods

Data for our study was obtained from the Nationwide Inpatient Sample 2001-2010. Standard descriptive methodology assessed characteristics of patients undergoing DBS and matched propensity score adjusted multivariate regression analysis evaluated outcome.

Results

Overall 45,966 patients who underwent DBS procedures were identified. The mean age was 52.49 years (SD=20.78). A total of 346 hospitals were identified in the NIS that performed DBS procedures. Hospital volume was categorized into low-volume (1-10/year), medium-volume (10-100/year) and high-volume (>100/year) hospitals, and represented 13.33%, 81.34%, and 5.33% respectively of the entire DBS caseload. Most procedures were performed in teaching hospitals (88.53%), centered in urban areas (96.83%), and in large bed-sized facilities (85.35%), and in the South (32.69%), and West (26.71%) regions. The most common diagnosis among patients undergoing DBS procedures was paralysis-agitans (46.57%). Assessment of complications did not reveal any significant association in the incidences of neurological (p=0.46) and/or infectious complications (p=0.11) with hospital volume. However, the incidences of mechanical complications demonstrated significant associations with hospital volume [i.e. high-volume vs. medium-volume. vs. low-volume (2.33% vs. 3.30% vs. 4.92%, p<0.001)]. Results of propensity-matched and multivariate adjusted analysis showed that compared to low-volume, medium-volume (OR=0.72; 95%CI=0.53-0.99, p<0.04) and high-volume (OR=0.43; 95%CI=0.22-0.85, p=0.02) were less likely for mechanical complications following DBS placement. Overall mortality was low (0.34%); however mortality was significantly reduced in high-volume and medium-volume compared to low-volume (0.21% vs. 0.23% vs. 1.05%, p<0.001) centers. Multivariate analysis revealed reduced odds of mortality in medium-volume (OR=0.28; 95%CI=0.14-0.56, p<0.001) and high-volume (OR=0.26; 95%CI=0.03-1.98, p=0.19) hospitals compared to low-volume hospitals.

Conclusions

This analysis suggests that hospitals with higher DBS caseloads provide superior short-term outcomes with reduced risks of mechanical complications following DBS placement.

515 Responsive Neurostimulation for Drug-Resistant Epilepsy: Analysis of Device Configuration and Neuromodulatory Effects

Nathaniel D. Sisterson; Vasileios Kokkinos; Thomas A. Wozny; Robert Mark Richardson

Introduction

Closed-loop neurostimulation is now an important treatment for drug-resistant epilepsy. Data informing treatment detection and stimulation parameters, however, are extremely limited. To overcome this barrier, we developed a novel platform for investigating responsive neurostimulation parameter space, event logging, and response to stimulation. Here, we describe the neuromodulatory effects of closed-loop stimulation on clinical and electrographic outcomes from the level of individual stimulation events.

Methods

Patient-reported outcomes in 12 subjects undergoing responsive neurostimulation were analyzed. In-depth analysis of parameter space and logging capabilities were undertaken using a novel computational platform, and seizure onset was marked in 14,394 90-second ECoG recordings by manual review. We then developed a method using weighted means to measure the bias created by the incompleteness of preserved ECoG recordings relative to overwritten and unstored recordings, as well as the existence of multiple seizure detection patterns. Finally, we performed a spectral analysis of ECoG recordings for each patient, aligned by seizure onset and grouped by time post-implant, to investigate the neuromodulatory effects of closed-loop stimulation.

Results

The average duration of responsive neurostimulation was 22 ± 10 months. The mean percentage of preserved ECoG recordings was 3% ± 7%. We found significant differences between weighted versus non-weighted means for accuracy, sensitivity, specificity, and latency of seizure detections. Spectral analysis revealed several modulatory effects, both transient and long-term, in response to ictal-like discharges (ILDs): frequency modulation of ILD oscillation, ILD fragmentation, increase of refractory epochs between consecutive discharges, decrease in mean ILD duration, and acute ILD inhibition.

Conclusions

Closed-loop parameter space and event logging is vast and complex. However, device configuration can be approached in a rational manner by evaluating settings using a weighted-mean methodology, which reduces the bias of ECoG reports. Furthermore, we identified, for the first time, several neuromodulatory mechanisms that may account for changes in clinical seizure manifestation.

516 Accuracy of Patient Registration: Avoiding Use of Multiple Bone Fiducials

David J. Donahue; John Harrell Honeycutt; M. Scott Perry; Laurie Bailey

Introduction

RATIONALE: Although the robot can be registered to the patient using surface landmark identification, we have come to prefer the accuracy provided by 5 "bone fiducials" affixed to the skull, which entails 9 scalp wounds entailed by 4 Leksell pins plus the 5 fiducials. We reasoned that employing the 4 pins securing the Leksell frame to the skull as fiducial points would obviate 4 of the bone fiducials without compromising accuracy..

Methods

We quantified localization error,defined as the euclidian distance between planned entry/target points and actual entry/target points, for each SEEG electrode trajectory associated with either Leksell Pin (LP) or "traditional" bone fiducial (BF) registration in the manner described by Gonzalez-Martinez et al.1 Target-point and entry-point errors of 70 consecutive LP-defined trajectories were compared to those seen for 95 consecutive BF-defined trajectories.

Results

Point errors were seen in 92 FP trajectories and in 67 LP trajectories. Target-point errors (TPE) for the LP group (median = 1.8mm, range 0 5.8) were similar to the BF group (median = 1.6 mm, range 0 7.8) with a mean difference of -.178t(163) = -1.541, p=.125, (90% CI, -0.369 to 0.013). Likewise, entry-point errors (EPE) for the LP group (median = 1.2, range 0 3.2) were similar to the BF group (median = 0.9mm, range 0 4.7) with a mean difference of -0.016 t(163) = -0.078, p=.938 (90% CI, -0.347 to 0.315).. Only one of the 67 LP entry-point errors exceeded 3.0 mm; 2 of the 95 BF entry-point errors exceeded 3.0mm.

Conclusions

The techniques appear equally accurate, but the LP bone fiducial renders placement of 4 bone fiducials unnecessary, potentially reducing OR time and patient discomfort

517 Pre-Operative Voxel Wise Morphometric Correlation with Post-Surgical Outcomes in Patients with Mesial Temporal Epilepsy

Mahdi Alizadeh; Benjamin Trieu; Lauren Kozlowski; Jennifer Muller; Solomon Feuerwerker; Christian M. Hoelscher; Feroze Mohamed; Ashwini Dayal Sharan; Chengyuan Wu

Introduction

Neurologic diseases, such as epilepsy, often cause long-term debilitation for patients leading to deficits in brain function and frequent seizures [1,2]. The purpose of this study is to determine if there are changes in gray matter concentration using voxel based morphometry (VBM) between mesial temporal lobe epilepsy (MTLE) responders and non-responders to the surgical treatments including either an anterior temporal lobectomy (ATL) or Selective Laser Amygdalohippocampectomy (SLAH).

Methods

A total of 18 patients with TLE (12 males, 6 females, with mean age and std of 46.18±13.8) underwent either ATL or SLAH and were scanned using T1 prior to surgery. 12 patients were responded to surgical treatments and 6 patients were still experienced seizure after surgery within 6 months follow up. All patients had a diagnosis of TLE according to standard clinical criteria. VBM was performed on T1 images using CAT12 and SPM12 toolboxes. Initially T1 images were normalized to a template space and segmented to the gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Before estimating statistical model, data was smoothed using median filter to minimize the effects of noise and WM/GM interface (figure 1). Finally, first level statistical module was designed based on paired t-test. In the statistical model, total intracranial volume (TIV) was used as a confound variable to correct for different brain sizes.

Results

Significant differences in GM concentration have been shown between responders and non-responders in 5 different regions. These regions are included contralateral middle temporal gyrus (111.38mm^3), contralateral caudate (23.63mm^3), ipsilateral dorsolateral prefrontal cortex (60.75mm^3)), ipsilateral supramarginal gyrus (81mm^3) and ipsilateral postcentral gyrus (54mm^3).

Conclusions

This type of analysis provides new insights for why some patients with TLE continue to experience postoperative seizures if pathological/clinical correlates are further confirmed. These preliminary results are very encouraging and warrant further studies with a larger population. The results show significant changes in regions outside the temporal lobe, in the areas that are connected to the limbic system specifically hippocampus and parahippocampal regions suggesting different configurations of epileptogenic networks in these 2 groups.

518 Stereoencephalography Electrode Placement Accuracy and Utility Using a Frameless Insertion Platform Without a Rigid Cannula

Erin D'Agostino; Yinchen Song; John Kanter; Joshua P. Aronson

Introduction

Implantation of depth electrodes to localize epileptogenic foci in patients with drug-resistant epilepsy can be accomplished by frame-based, frameless, and robotic stereotactic systems. We aim to evaluate the accuracy of electrode implantation using the FHC microTargeting platform without use of a rigid insertion cannula.

Methods

A total of 147 depth electrodes were implanted in eleven patients who underwent stereoelectroencephalography (SEEG) for drug-resistant epilepsy using the microTargeting platform and Ad-Tech depth electrodes without rigid guide cannula. MATLAB was utilized to evaluate targeting accuracy. Two manual coordinate measurements were averaged with minimal inter-rater reliability.

Results

Patients were predominantly male (91%) with average age 35.3 (SD 11.1, range 21-57) and average age of epilepsy onset at 14.1 (SD 7.6, range 3-26). On MRI, 27.3% were noted to have structural abnormalities and 18.2% to have hippocampal sclerosis. 27.3% of patients underwent depth electrode placement due to bilateral ictal scalp EEG activity, 27.3% due to delay or absence of EEG activity following clinical manifestation, and 36.4% due to competing potential seizure foci. A mean of 13.5 electrodes were implanted (range 10-16). Mean operative time was 146 minutes (range 104 to 176). One patient developed a post-operative complication. Location of onset was identified in all patients, though one patient required implantation of an additional electrode. Mean lateral entry point localization error was 1.78 mm (sd 3.23) and mean lateral target point localization error was 2.45 mm (sd 1.79). Following monitoring, 63.6% underwent RNS placement, 27.3% underwent temporal lobectomy, and 9.1% underwent other focal resection. At follow up (mean 4.6 months, range 1.7-9.8), 54.5% of patients demonstrate an Engel class I outcome.

Conclusions

Utilization of the FHC microTargeting platform without the use of insertion cannulae is safe, effective and accurate. Localization of seizure foci was accomplished in all patients and accuracy of depth electrode placement was satisfactory.

519 Functional Network Organization Correlates with Duration of Temporal Lobe Epilepsy

Elliot G. Neal; Stephanie Maciver; Fernando L. Vale

Introduction
Previous studies have shown brain network disturbances in patients with epilepsy. A software algorithm that models resting state networks using non-invasive and non-concurrent data is desirable for identification of epileptic networks. Using our novel network modeling algorithm, we observed patterns in resting networks suggesting possible differences between patients with regards to age, epilepsy duration, and presence of mesial temporal sclerosis (MTS) that may lead to better identification of surgical candidates and resection targets.

Methods
Eleven patients with temporal lobe epilepsy were prospectively included. Resting-state functional MRI and scalp EEG were recorded and pre-processed. EEG sources were localized using a Bayesian approach to the fixed dipole inverse solution. Component time series functions correlating to the inter-ictal source localization volume were mapped.

Results
Global connectivity (Pearson correlation) was not significantly different between the epilepsy cohort and age-matched healthy controls. Connectivity was higher in younger patients with epilepsy and in patients with shorter epilepsy duration (<10 years). However, spatial distribution of the epilepsy networks in these young patients was more variable than those in older (30+ years-old) patients with longer-standing epilepsy (10+ years). Network spatial variability was also increased in patients without MTS compared to those with MTS.

Conclusions
We developed a novel multi-modal, non-invasive epilepsy network modeling algorithm and present here our preliminary observations. We found that younger patients with more recent epilepsy onset had network connectivity patterns that were highly variable, and network structure became more consistent between patients with time. It is possible that individual patients have brain networks that reorganize at different rates, which could explain the early variability in network spatial distribution and connectivity. Future studies aim to compare surgical outcomes to the observed variable patterns in network reorganization to investigate the role of network analysis in pre-operative planning and inform more personalized, targeted surgical interventions for treatment of intractable epilepsy.

520 Effect of Advancing Age on Complication Rates Following Epilepsy Surgery

Stephen C. Harward, II; Robert Gramer; Siyun Yang; Jichun Xie; Shervin Rhamipour; Max Ostrinsky Krucoff; Dario J. Englot; Shivanand P. Lad

Introduction

Historically, epilepsy surgery has not been offered to patients of advanced age because of concerns for increased rates of post-operative complications and morbidity. Although no specific age cutoff has been defined, many clinical studies have excluded patients older than 50 years. Presently, there is no definitive data to support this practice. As such, our group investigated the effect of advanced age on complication rates following epilepsy surgery. We hypothesized that increasing age would be associated with an increased number of postoperative complications.

Methods

Using the Truven MarketScan database, we performed a large, retrospective, cohort study of patients 18 years or older who underwent epilepsy surgery between the years 2000 and 2011. We examined both aggregate and individual post-operative complications. Additionally, multivariate logistic regression analysis was employed to determine complication-related odds ratios for both advanced age (age 50 years or older) and increasing 5-year age epochs after adjusting for other covariates.

Results

Overall, 84 of 709 patients had a complication within 90 days of surgery. These included intracranial hemorrhage or hematoma (52 patients, 7.3%), infection (33 patients, 4.7%), pneumonia (10 patients, 1.4%), and pulmonary embolism (9 patients, 1.3%). After controlling for covariates, we found that except for pneumonia, advanced age and increase age (5-year epochs) did not correlate with higher 90-day incidence of post-operative complications (OR 1.11; 95% confidence interval 0.59-2.11; p = 0.744).

Conclusions

Older patients selected for epilepsy surgery showed a similar 90-day complication risk compared with their younger cohort. As such, our results suggest that age should not be a primary factor in determining one's candidacy for epilepsy surgery. Instead, a clear focus on patients with medication-refractory epilepsy and their candidacy for a variety of newer neuromodulation, neuroablative and neurosurgical treatment options should allow for expansion of the traditional therapeutic window.

522 Ex-vivo Retrograde Transport in Rat and Human Cortex: A Model for Cortical Connectivity

Alexander Ksendzovsky; Alexander Tolpygo; Stuart Walbridge; Daniel Ferrante; Jeffrey Diamond; Partha Mitra; Kareem A. Zaghloul

Introduction

There are currently no molecular techniques to visualize human cortical connectivity. Several in vivo methods (axonal tracing) have been developed but are limited to animal use only. Resected human cortical tissue from epileptic patients is potentially amenable to these techniques and can be used to study cortical connectivity. In this study we describe a rat model of ex vivo retrograde transport (RT) to characterize cortical connectivity. This model serves as the basis for axonal tracing in resected human cortical specimens.

Methods

Resected human temporal cortex and motor cortex (M1) or CA1 of 3mm coronal rat brain sections were injected with 100nL and 50nL 2% cholera-toxin subunit-b (CTB), respectively. Tissue was maintained at 25? and 32?C on a patch-clamp stage with continuously circulating carbogenated artificial cerebrospinal fluid (cACSF) (rate of 3mL/min or 6mL/min) for 4, 24, 48 and 96hrs. Tissue blocks were sectioned, stained and analyzed for axonal transport using cell counting, injection volume and length of axonal transport. In vivo rat studies were used to corroborate axonal transport. Tissue toxicity and ischemia were analyzed with H&E staining of the sections above.

Results

Resected tissue was successfully kept alive ex vivo, which allowed CTB transport to occur. This was confirmed with retro-2, a small molecule RT inhibitor. Longer incubation times, 32?C stage temperature and 6mL/min cACSF yielded a statistically significant increase in RT. At 72 and 96 hours, cells were traced to the contralateral M1 and thalamus with transport across the corpus callosum and thalamocortical radiations. CA1 injections yielded RT to CA3 along Schaffer's collaterals in rat. Injected human tissue demonstrated specific cortico-cortico projections with RT and tagged cells in up to 1cm of tissue.

Conclusions

In this study we present a novel ex vivo method of axonal tracing in rat and human cortical tissue. Ex vivo RT is currently being used to define cortical structure in resected epileptic and normal human cortex.

523 Cortical Thickness in Associative Cortical Areas may Play a Role in the Prediction of the Motor Outcomes after DBS for Parkinson's Disease.

Leonardo A. Frizon; Raghavan Gopalakrishnan; Olivia Hogue; Sean J. Nagel; Gustavo Rassier Isolan; Andre Machado

Introduction

STN DBS is a widely accepted therapy for Parkinson´s disease patients. While clinical predictors for satisfactory outcomes of this therapy have been widely studied, there is scarce literature reporting imaging predictors. Cortical thickness is associated with neuronal structural complexity features such as neuronal size, dendritic arborization and presynaptic terminals. The primary aim of this study was to perform a broad review of cortical thickness measures and postoperative outcomes to generate hypotheses for future investigations.

Methods

Patients who underwent bilateral STN-DBS for Parkinson´s disease at our institution between 2013 and 2016 were included. Movement Disorders Society Unified Parkinson Disease Rating scale motor subscale (MDS-UPDRS III) and motor aspects and experiences of daily living subscale (MDS-UPDRS II) were collected at the baseline and six months after DBS surgery. Cortical reconstruction and volumetric segmentation were performed using FreeSurfer image analysis suit based on pre-operative MRI 3T T1-images. Mean cortical thickness from predefined areas were obtained from automatic cortical segmentation of the total brain volume.

Results

Thirty-five patients had available pre- and postoperative MDS-UPDRS-III scores, and 25 patients had available pre-and postoperative MDS-UPDRS-II scores. Lateral-occipital areas in the right and left hemispheres displayed negative correlations with the total motor score after surgery, with a strong correlation on the left side and a moderate correlation on the right side. Other areas such as pars opercularis, posterior cingulate, superior temporal, lateral orbito-frontal, transverse temporal and insula displayed moderate negative correlations with the motor outcome. Some of these areas are included or related to the "mirror neuron system", involved in action observation and action execution according to circumstances. Negative correlations were observed between the anterior cingulate areas, superior frontal, caudal middle frontal, medial orbitofrontal, parahippocampal, transverse temporal areas and MDS-UPDRS II.

Conclusions

Our data indicate that cortical thickness in associative cortical areas may predict outcomes after DBS surgery.

524 Tractography profiles associated with treatment response to radiosurgical capsulotomy for obsessive-compulsive disorder

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Introduction

Stereotactic radiosurgical (SRS) lesioning of the anterior limb of the internal capsule remains a treatment option for patients with treatment-resistant obsessive-compulsive disorder (OCD). However, mechanisms behind response remain unclear. To probe whether lesions placed in specific white-matter tracts were related to response, we determined the connectivity profile of responsive vs non-responsive lesions.

Methods

Bilateral lesions from 16 OCD patients who underwent SRS ventral capsulotomy were hand-traced and then warped to MNI space. Individual patient volumes were labeled responder or nonresponder based on Yale-Brown Obsessive Compulsive Scale (YBOCS) change from baseline. Composite lesion volumes were created from voxels where >50% of lesion overlap occurred. As only post-surgical scans were available for lesion tracing, a separate cohort of 7 OCD patients was used for tractography analysis. Probabilistic tractography was performed between all Freesurfer-segmented anatomical ROIs and individually warped capsulotomy lesion volumes. The connectivity of responder and nonresponder lesions to ROIs (number of tracts) was compared for the cortical and subcortical ROI with the highest connectivity difference.

Results

The YBOCS change of responders (-23.6 ± 7.2) and nonresponders (-9.8 ± 3.5) differed significantly ($p<0.001$). The responder composite centroid was lateral to the midline (Left: 15.2 mm, Right: 13.9 mm), anterior to the anterior commissure (L: 12.7 mm, R: 12.8 mm), and inferior to the AC-PC plane (L: 5.3 mm, R: 5.2 mm). Compared to nonresponders, left responder composite volumes had significantly greater connectivity to the ipsilateral caudate ($p=0.011$) and medial orbitofrontal sulcus ($p=0.029$). Right responder volumes had significantly greater connectivity to the ipsilateral putamen ($p=0.009$), and nonsignificantly greater connectivity to the ipsilateral gyrus rectus ($p=0.311$).

Conclusions

Preliminary tractography analysis of SRS capsulotomy lesions suggests that more clinically effective lesions are located within medial orbitofrontal-striatal loops, whose altered connectivity has been thought to underlie OCD symptoms. These results can help optimize lesion placement in future studies.

525 Propofol-induced Loss of Consciousness is Associated with a Decrease in Directly Measured Thalamocortical Connectivity

Collin M. Price; Mahsa Malekmohammadi; Nicholas Au Yong; Evangelia Tsolaki; Andrew E Hudson; Nader Pouratian

Introduction

Although the molecular effects of many anesthetics have been well characterized, a network-level explanation for how these lead to loss of consciousness remains elusive. Studies utilizing electroencephalography have characterized changes in neural oscillations at specific frequency bands during Propofol-induced anesthesia, and recent modeling work suggests these changes result from altered communication between the thalamus and cortex. However, direct recordings from these sites during anesthesia is rare.

Methods

We recorded local field potentials from the ventral intermediate nucleus (ViM) of the thalamus and electrocorticography signals from the ipsilateral sensorimotor cortex in seven patients undergoing deep brain stimulation surgery. Signals were acquired during induction of Propofol anesthesia while subjects were resting. After confirming direct structural connectivity between ViM and the cortical recording site, we investigated Propofol associated changes in intrathalamic and intracortical power, as well as thalamocortical coherence, phase lag index (PLI), and phase amplitude coupling.

Results

At all nodes Propofol anesthesia resulted in a local power increase at alpha frequencies (8-12 Hz). At sensorimotor cortices there was a broadband power increase (12-100 Hz), while the power of this same broad frequency band was suppressed at ViM. The post-anesthesia state was associated with significantly decreased coherence and PLI between the thalamus and cortex (with thalamus leading) in the alpha/low beta frequencies (8-16 Hz, $P<0.05$, two group test of coherence), as well as decreased coupling between the phase of alpha/low beta in the thalamus and the amplitude of broadband gamma (50-200 Hz) in the cortex ($P=0.031$, Wilcoxon signed-rank test).

Conclusions

Our results show that changes in the alpha band in the thalamus consistently led the sensorimotor cortices, and the two signals were coherent. Despite local alpha power increases, we observed a decrease in thalamocortical connectivity after anesthesia, in support of the theory that Propofol-induced loss of consciousness is associated with disrupted thalamocortical communication.

526 Magnetic Resonance Fingerprinting for Target Identification in Deep Brain Stimulation

Dan Ma; Angela M. Noecker; Mark Griswold; Cameron C. McIntyre

Introduction

Traditional MRI acquisitions are restricted to qualitative "weighted" measurements of tissue properties where the signal intensities are dependent upon many factors, including the type and set-up of the scanner. Magnetic Resonance Fingerprinting (MRF) is a revolutionary new approach to collecting and analyzing MRI data that permits simultaneous quantification of multiple tissue properties (e.g. T1 and T2).

Methods

MRF uses a pseudorandomized acquisition that causes the signals from different materials or tissues to have a unique signal evolution or 'fingerprint' that is simultaneously a function of the multiple material properties under investigation. MRF processing after acquisition involves a pattern recognition algorithm to match the fingerprints to a predefined dictionary of predicted signal evolutions. These can then be translated into quantitative maps of the magnetic parameters of interest.

Results

We used MRF in a Siemens 3T scanner to collect a fully quantitative 3D image of a whole human brain within a Leksell Vantage MRI compatible stereotactic frame. T1, T2, and proton density maps were created at 1.2 mm isotropic resolution. Basic tissue clusters were then calculated using k-means analysis and used to segment anatomical structures within the subthalamic region. The whole brain MRF scan time was less than 12 min, including a B1 mapping scan to correct for inhomogeneity, making acquisition of these quantitative MRI measurements clinically plausible.

Conclusions

MRF represents a new imaging tool that can quantitatively standardize MRI-based tissue segmentation and surgical target identification.

527 Biomechanical Modeling of Brain Shift in Deep Brain Stimulator Placement Surgery

Chen Li; Xiaoyao Fan; Joshua P. Aronson; Keith Paulsen

Introduction
The efficacy of deep brain stimulation (DBS) depends on accurate placement of electrodes. Although stereotactic guidance systems reduce motion between patient and electrodes at the skull, the accuracy of pre-operative planning can be degraded by intra-operative brain deformation. We compensate for such shift by utilizing a biomechanical model to estimate a whole brain displacement field and generate an updated CT (uCT) by transforming preoperative scans, accordingly.
Methods
We evaluated 6 patients who underwent bilateral DBS placement and assessed the accuracy of our model. Pre-operative CT (preCT) and post-operative CT (postCT) were used to generate displacement fields of the brain surface at the interface with pneumocephalus using an iterative closest point (ICP) algorithm. These sparse data were assimilated into a biomechanical model to generate uCT with shifted sub-cortical structures. Anterior commissure (AC) and posterior commissure (PC) points were identified on preCT and postCT and used to quantify target registration errors (TREs) in the original preCT and uCT. TREs were further decomposed into three orthogonal directions with respect to the commissural plane.
Results
Average TREs for uCT were 1.32±0.46 and 1.76±0.82 mm at AC and PC, respectively, compared to 1.95±0.37 and 1.64±0.8 mm for preCT.
Conclusions
Our model-based image updating approach based on intra-operative sparse data reduced TREs at AC to be less than 1.5 mm on average. The model did not alter TREs at PC; however, incorporating additional information from deep structures such as the ventricles in to the sparse data assimilation is expected to improve model prediction. These results support the utility of sparse data assimilated through biomechanical modeling to predict brain shift and may be incorporated into intraoperative planning to improve DBS targeting accuracy.

528 A Novel Mesial Temporal Stereotactic Coordinate System

Kai Joshua Miller; Casey H. Halpern; Mark Sedrak; John A. Duncan, III; Gerald A. Grant

Introduction

Stereotactic laser ablation and neurostimulator placement represent an evolution in staged surgical intervention for epilepsy. As practice evolves, optimal targeting will require standardized outcome measures that compare electrode lead or laser source with post-procedural changes in seizure frequency. We propose and present a novel stereotactic coordinate system based upon mesial temporal anatomic landmarks to facilitate the planning and delineation of outcomes based on extent of ablation or region of stimulation within mesial temporal structures.

Methods

The body of the hippocampus contains a natural axis, approximated by the interface of CA4 and the dentate gyrus. The uncal recess of the lateral ventricle acts as a landmark to characterize anterior-posterior extent. Several volumetric rotations are quantified for alignment with the hippocampal coordinate system. First, the brain volume is rotated to align with standard AC-PC space. Then, it is rotated through the axial and sagittal angles the hippocampal-axis makes with the AC/PC-line.

Results

Using this coordinate system, customized MATLAB software was developed to allow for intuitive standardization of targeting and interpretation. The angle between the AC/PC-line and the hippocampal-axis was found to be ~20-30° when viewed sagittally and of order ~-5-10° when viewed axially. Implanted electrodes can then be identified from CT in this space, and laser tip position and burn geometry can be calculated based on the intraoperative and post-operative MRI.

Conclusions

With the advent of stereotactic surgery for mesial temporal targets, a hippocampal stereotactic system is introduced which may facilitate operative planning, improve surgical outcomes, and standardize outcome assessment.

529 Interictal Cross-frequency Windowed Power-power Coupling Differentiates Epileptic Regions from Voluntary High-gamma Activation

Michael Kogan; David Caldwell; Kurt Weaver; Andrew Lin Ko; Jeffrey G. Ojemann

Introduction

High gamma signals are a known proxy for local brain activation, however, newer research evaluating interactions between frequencies suggest that modulation of high-gamma by lower bands modulates both local and remote activity. Our aim is to investigate amplitude-amplitude coupling in the context of motor and language tasks to identify functionally connected regions.

Methods

Three epilepsy patients were included who had previously undergone left subdural grid implantation at our institution who participated in motor and language tasks. The data was recorded on a with g.USBamps (GugerTec) sampled at 1200 Hz with hardware imposed filters set at 0.1 Hz (high pass) and 500 Hz (low pass) with a notch filter set at 60 Hz. Both the motor paradigms and picture-naming tasks were completed using the general-purpose BCI2000 stimulus and acquisition program. All data analyzes were conducted in MATLAB computing environment. we used a sliding window approach from beginning of activity to end of rest. We computed amplitude-amplitude coupling using a 4th order Butterworth to bandpass signals to corresponding high gamma (70-200 Hz) and beta (12-18 Hz) frequency bands for each individual epoch. We estimated amplitude envelope using a smoothed Hilbert transform. A one sample t-test determined the significance for each window, which we compared spatially using the entire activity and rest period.

Results

Amplitude-amplitude coupling demonstrated an overall spatial distribution of high gamma/beta correlations that did greatly vary according to task. However, the total time of correlation varied between electrodes in a manner that appeared consistent with known physiology.

Conclusions

This preliminary study suggest that the distribution of amplitude-amplitude coupling does not vary between tasks, however, the degree of coupling seems to vary regionally between motor and language activities. Our next aim is to further characterize and quantify this effect as well as investigate the connectivity of task specific areas.

530 Development and Validation of a Simple Landmark Placement Protocol for Establishing Correspondence Between Brain Images

Jonathan C. Lau; Andrew G. Parrent; John Demarco; Ali R. Khan; Terry M. Peters

Introduction

Template and atlas-guidance are fundamental aspects of stereotactic neurosurgery. Accurate spatial correspondence between the template and patient images is a crucial step in being able to use templates to assist with surgical implantation. In the absence of a robust quantitative approach, we sought to propose and validate a set of point landmarks that could be quickly, accurately, and reliably placed on brain images.

Methods

A series of neuroanatomical landmarks were identified in consultation with an experienced neurosurgeon. Consensus was achieved on a set of 32 landmarks (Figure 1). Over a series of neuroanatomy tutorials, novice participants (N=8) were trained to perform the protocol on 3 publicly available brain templates: Colin27 [1], MNI2009b [2], and Agile12v1.0 [3]. For each template, our participants placed the landmarks four times (384 landmarks/participant). Fiducial localization error (FLE) was calculated to establish reliability. We performed K-means clustering on the principal components of the landmark-specific point clouds.

Results

Intra- and inter-rater reliability were 1.24 +/- 0.17 mm and 1.24 +/- 1.94 mm respectively. Out of 3258 landmarks placed, there were 24 (0.74%) outliers more than 10 mm from the group mean, which we classified as mislabeled and thus discarded. Significant differences in FLE were identified between templates (Colin27: 1.11 +/- 1.05 mm; MNI2009b: 0.95 +/- 0.82 mm; Agile12v1.0: 1.02 +/- 0.94 mm). K-means clustering of the principal components identified three clusters (Figure 2). Landmark placement time was estimated at 30 minutes.

Conclusions

Our landmarks provide an intuitive and anatomically-driven framework for establishing quality of registration between brain images. While overall FLE was within an acceptable range, point cloud distributions were heterogeneous. The proposed protocol is reproducible, less manually intensive, and more sensitive to local errors than segmentation-based or qualitative evaluation of correspondence. This may hold value for a broad number of applications including template-to-patient registration and teaching neuroanatomy.

531 Brain Mapping, Lesion Size, Tremor Suppression, and Side Effects with MR-guided Focused Ultrasound Thalamotomy: Early Results

Zelma HT Kiss; Robyn Warwaruk-Rogers; Erin Mazerolle; G. Bruce Pike; Tejas Sankar; Samuel Pichardo; Menashe Zaroor; Davide Martino

Introduction

MR-guided focused ultrasound (MRgFUS) is a new way to perform thalamotomy for essential tremor (ET). It is unknown whether ultrasound-based thalamic mapping can help with targeting, or how lesion size and placement will affect tremor and side effects. Therefore with this prospective trial of MRgFUS thalamotomy, we AIM to optimize targeting, lesion size, and location.

Methods

Patients, diagnosed with ET by a movement disorder neurologist, who have failed medications and pass neuropsychology and CT screening are enrolled. Assessments consisting of accelerometry, Clinical Rating Scale for Tremor (CRST), ataxia scale, Purdue pegboard, depression, and quality of life scales are performed pre, post- at month 3 and yearly thereafter. MRI is performed at these time points, as well as on day 1 post-op. Initially we used the targeting suggested by the manufacturer, based on atlas Vim, 14 mm lateral to midline on the AC-PC line. We are recently trying lower temperature verification methods to map somatosensory thalamus before moving to the lesioning target.

Results

Nine patients (8 M, 1 F) have had MRgFUS thalamotomy (2 R, 7 L). The number of sonications ranged from 13-24. All patients experienced "flipping backwards" during sonications that improved tremor. In 3 of 5 patients where we performed sonications 2-4 mm posterior to target, we observed face paresthesia. Five have reached 3-month follow-up and have 27-93% improvements in CRST. Average lesion volumes at day 1 (from T1 and SWAN images) ranged from 159-478 mm3 and were unrelated to tremor outcome. Adverse effects included feeling off balance, contralateral clumsiness, taste changes, numbness in the hand or mouth, and in one patient the emergence of myoclonus.

Conclusions

Our early results are similar to those reported in larger series. Ongoing research will determine the relationship of lesions to brain atlases, use pre-operative tractography, and test neuromodulatory sonications to tailor targeting in each patient.

32 Robot-Assisted Stereotaxy Minimizes Target Error: A Meta-Analysis of 8,902 Trajectories

Sara Thalheimer; Ashwini Dayal Sharan; Chengyuan Wu

Introduction

Despite a growing number of frame-based, fiducial-based, and robot-assisted stereotactic methods, accuracy remains the driving force behind stereotaxy. At present, a direct comparison of all stereotactic methods has yet to be performed. The present study serves as a meta-analysis of 26 publications, reporting the overall accuracy of frame-based and skull fiducial-based systems, and further takes into account the influence of robot-assistance.

Methods

A PubMed search was performed for the following terms: "Leksell," "Cosman-Robert-Wells," "CRW," "NexFrame," "STarFix," "ClearPoint," "NeuroMate," "ROSA," "accuracy," and "error." No date restrictions were placed. Raw accuracy data was extrapolated and recorded. System-specific accuracy means and standard deviations were calculated; and z-scores were calculated to compare differences between each system.

Results

Across 24 studies and a total of 8,902 measurements, the average Euclidean target error for frame-based, fiducial-based, and robot-assisted procedures was 1.89 ± 1.12 mm (N = 2249), 1.86 ± 1.03 mm (N = 1630), and 1.72 ± 0.71 mm (N = 5023), respectively. These data yield no statistical difference between frame-based and fiducial-based systems ($p = 0.37$), however, the use of a robotic system yielded a statistically significant increase in target accuracy ($p < 0.001$). Furthermore, when examining only clinically-derived measurements, fiducial-based systems demonstrate a statistically significant increase in accuracy over frame-based systems ($p < 0.001$), with mean target errors of 2.20 ± 1.26 mm (N = 1070) versus 2.47 ± 1.42 mm (N = 449), respectively. Still, robot-assisted procedures were reported to have the greatest accuracy ($p < 0.001$), with a mean target error of 1.92 ± 0.92 mm.

Conclusions

There are incremental improvements from frame-based to fiducial-based and from fiducial-based to robot-assisted of 0.28 mm and 0.27 mm, respectively. All systems demonstrated a mean Euclidean target error of <2.5mm and have demonstrated the ability to provide reliable electrode placement.

533 Accuracy and Predictability in Stereotactic Stem Cell Transplantation

David Isaac Satzer; Regan O'Connor; Peter C. Warnke

Introduction

Multiple experimental therapies have employed stereotactic intracerebral transplantation of stem cells. However, stereotactic injection techniques have received little critical attention, and use of intraoperative CT guidance and accuracy of implantation has not been reported. This is critical for sophisticated stem cell applications which target highly eloquent small nuclei of the brain, for example.

Methods

Ten patients with history of ischemic stroke underwent CT-guided stem cell transplantation, as part of an ongoing clinical trial. Cells were delivered along 3 tracts adjacent to the stroke bed. Intraoperative air deposits and postoperative T2-weighted MRI signal were mapped in relation to surgical targets using Euclidian distances.

Results

The deepest air deposit was found 4.5 +/- 1.0 mm (mean +/- 2 SEM) from target. The apex of the T2-hyperintense tract was found 2.8 +/- 0.8 mm from target. On average, air pockets were found anterior (1.2 +/- 1.1 mm, $p=0.04$) and superior (2.4 +/- 1.0 mm, $p<0.001$) to the target; no directional bias was noted for the apex of the T2-hyperintense tract. Location and distribution of air deposits was variable, and was affected by relationship of cannula trajectory to stroke cavity.

Conclusions

Precise stereotactic cell transplantation is a little-studied technical challenge. Reflux of cell suspension and air, and the extracellular space of the target structure, affect accuracy and assessment of delivery. However, intraoperative CT allows confirmation of delivery, assessment of the boundaries of delivery, and potential correction of trajectories.

534 Identification of Cingulum Bundle Connectivity Using Tractography: Are Animal Studies Still Necessary?

Jennifer A. Sweet; Suraj Thyagaraj; Eric Herring; Jesse Drapekin; Keming Gao; Jonathan Miller; Cameron C. McIntyre

Introduction

Tractography has emerged as a potentially significant imaging modality to visualize white matter (WM) tracts within the brain. However, its accuracy, relative to anatomical tract-tracing, has long been questioned. This study aims to replicate, in human subjects, an animal axonal tracing study (Heilbronner and Haber, 2014) investigating the cingulum bundle (CB), a WM tract implicated in the pathophysiology of psychiatric disorders, using several tractography techniques, to determine the validity of tractography compared to animal tracing models, and to better understand current and future neurosurgical targets for intervention.

Methods

Healthy volunteers underwent 3T T1 and diffusion-weighted MRI sequences. Regions of interest were created to replicate an anatomical tract-tracing study done in non-human primates. Tractography was performed using three different techniques (FSL probabilistic, Camino probabilistic, and Camino deterministic). Differences in connectivity were assessed, and the CB segment with the greatest connectivity was determined.

Results

Five subjects were included. Each tractography technique successfully reproduced the findings of the animal tracing study, but with greater accuracy and detail. The region of CB found to have the greatest connectivity was the rostral dorsal CB.

Conclusions

Analysis of the CB using multiple tractography methods in human subjects consistently reproduced the results of an animal tract-tracing model, while providing more detailed connectivity information. This demonstrates the validity of tractography in assessing WM tract connections and suggests a superiority to animal tracing model correlates. In addition, the findings reveal that the rostral dorsal CB has greater connectivity than other CB segments to brain regions thought to be involved in psychiatric disorders, which may have far-reaching implications for surgical targeting.

535 Deep Brain Stimulation Improves Restless Legs Syndrome in Patients with Parkinson's Disease

Olga Klepitskaya; Ying Liu; Sharma Saloni; Stefan H. Sillau; Jean Tsai; Arthur S. Walters

Introduction

Restless legs syndrome (RLS) is a very common sensorimotor neurologic disorder. The impact of RLS on patients' quality of life cannot be underestimated. Although there are multiple effective treatment options for RLS, in some cases RLS symptoms remain refractory to all known therapeutic modalities. In this study we aimed to study the effect of STN DBS in the largest cohort of patients with Parkinson's disease and moderate to severe RLS, reported in the literature to-date, on their RLS symptoms.

Methods

Patients, undergoing STN DBS surgery for PD, completed the International RLS Study Group rating scale (IRLS) and the RLS Quality of Life (QoL) questionnaires pre-operatively and post-operatively at 6 months, 1 and 2 years. Primary outcome measure was IRLS sum score and subscales (severity and impact) and the secondary were RLS QoL scores, and rate of responders, remitters, and complete remitters. Differences among the mean scores over time were analyzed using mixed model regression.

Results

22 patients were enrolled. The preoperative IRLS sum scores were 19.59±6.95, severity subscale 12.91±4.33, impact subscale 4.45±2.72, and transformed RLS QoL score 68.30±20.26. The differences between pre- and averaged post-operative scores were: IRLS sum score -7.80, severity subscale -5.50, impact subscale -1.20, and RLS QoL 4.73. The overall F tests demonstrated differences among the times for the means of the IRLS sum and subscales: $p<0.05$. There was no significant correlations between RLS symptoms improvement and PD motor symptoms improvement or reduction in PD medications. Rate of responders was 50%, remitters 50%, and complete remitters 27.3%.

Conclusions

STN DBS significantly decreased RLS symptoms in PD patients despite a decrease in dopaminergic treatment. This improvement was sustained over a two-year period. These data suggest that STN DBS could be effective for treatment for medications refractory RLS.

536 Do Effects of DBS on Network Activity in Parkinson's Disease Vary Based on Phenotype?

Marisa D. DiMarzio; Radhika Madhavan; Suresh Joel; Ileana Hancu; Eric Fiveland; Julia Prusik.; Michael Gillogly; Jeffrey Ashe; Tanweer Rashid; Ilknur Telkes; Jennifer Durphy; Roy S. Hwang; Era Hanspal; Julie G. Pilitsis

Introduction

Deep brain stimulation(DBS) is a treatment of Parkinson's disease(PD) treating both tremor-dominant(hyperkinesia) and akinesia-rigidity(AR) dominant phenotypes 1. Despite variability in clinical manifestations, whether DBS modulates network activity differently in these phenotypes remains unknown. A conditional change in DBS labeling allows MRI to be performed with DBS-ON. Here we analyze whether network activity varies in PD patients depending on phenotypes.

Methods

The current study involved 17 patients diagnosed with PD. Subjects, independent from DBS target, were classified into tremor/AR cohorts based on dominant PD symptoms. Subjects with clinically optimized DBS programming underwent fMRI scans with their neurostimulator cycling between ON/OFF. To ensure that fMRI and programmer were synchronized, an electronics box was integrated into the workflow2. Voxel-wise General Linear Model(GLM) using DBS-OFF data was used to determine altered regions during DBS-ON. For group analysis, previous outputs of individual subjects were used to determine voxel-wise statistics. A multiple regression connectivity analysis was performed on data from individuals to determine connections of the motor circuitry.

Results

Individual fMRI analysis revealed that 5/6 tremor subjects had anterior cerebellum and thalamic activation, 4 had motor cortex(M1) deactivation. These findings were in contrast to the AR-cohort where 5/11 subjects had M1 activation, rather than deactivation($p<0.05$) and an equal amount had cerebellar activation/deactivation. Thalamic activation was similar between phenotypes. Group analysis of the tremor-cohort confirmed significant anterior cerebellar and thalamic activation, and M1 deactivation. AR group analysis confirmed M1 and thalamic activation. Connectivity studies revealed motor cortex to cerebellum connections in the tremor group, but not in the AR-cohort.

Conclusions

These data suggest that DBS modulates network activity differently in PD based on patient phenotype. An improved understanding of tremor/akinesia-rigidity differences and their functional roles in PD may allow us to exploit these connections to design more efficient personalized DBS therapy, hopefully, with better clinical results and less side effects.

537 Characterization of Prefrontal Cortical Activity During Emotional Face Processing in Movement Disorders Patients

Witney Chen; Coralie de Hemptinne; Andrew M. Miller; Paul S. Larson; Daniel A. Lim; Sheila Rajagopalan; Philip A. Starr

Introduction

Parkinson's disease (PD) patients have deficits in "theory of mind", the ability to infer thoughts and feelings in others. The dorsolateral prefrontal cortex (dlPFC) and the orbitofrontal cortex (OFC) are thought to be involved in theory of mind processing. However, emotional processing-related activity in these prefrontal regions is still poorly characterized in PD patients. In this exploratory study, we used high resolution, intraoperative electrocorticography (ECoG) targeted to various prefrontal areas to investigate the neural correlates of emotional face processing in PD and non-PD patients.

Methods

6 PD, 4 essential tremor, and 1 dystonia patient undergoing awake deep brain stimulation surgery were enrolled in this study. A 28 contact, high-resolution ECoG strip was temporarily placed over dlPFC, OFC, and/or inferior frontal cortex. Patients performed 50-100 trials of a go/no-go emotional face processing task in which images of three emotion types were presented: happy, sad, or neutral face images. For happy or sad faces, patients were instructed to press a button, while for neutral faces, patients withheld movement. We assessed task-related activity in PD and non-PD patients to characterize differences in cortical activity during emotional face processing.

Results

PD vs. non-PD patients have differences in task-related neural responses: 1) PD patients have less task-modulated theta in the dlPFC and OFC than non-PD patients. 2) Task-related gamma power is greater in the dlPFC of PD patients than non-PD patients.

Conclusions

Modulation of theta frequencies in the dlPFC and OFC may be related to emotional face processing in non-PD patients. PD patients have weaker theta modulation during the task, potentially due to excessive synchronization of neural activity to the beta band. This may be a pathophysiological signature of theory of mind deficits.

538 Pallidal Deep Brain Stimulation Disrupts Phase Coherence Between Globus Pallidus and Primary Motor Cortex in Parkinson's Disease

Doris D. Wang; Coralie de Hemptinne; Jill L. Ostrem; Nicholas Galifianakis; Marta San Luciano Palenzuela; Philip A. Starr

Introduction

Excessive beta (13-30 Hz) oscillatory activity in the basal ganglia thalamocortical network has been proposed as a biomarker for the parkinsonian state, based on the finding that reduction of beta oscillations in the basal ganglia by levodopa and deep brain stimulation (DBS) correlates with motor symptom improvement. Two prior studies comparing pallidal local field potentials (LFPs) between Parkinson's disease (PD) and non-parkinsonian conditions supported a relative increase in beta band oscillatory activity in PD, but it is not clear how these differences affect cortical function.

Methods

In 20 PD and 14 isolated dystonia patients undergoing pallidal DBS lead implantation, we recorded LFPs from the globus pallidus (GP) and in a subset of these, recorded simultaneous sensorimotor cortex electrocorticography (ECoG) potentials.

Results

PD patients had higher pallidal resting low beta (13-30 Hz) band power compared to dystonia patients, whereas dystonia patients had higher theta (4-8 Hz) resting power compared to PD. We show that this results in disease-specific patterns of interaction between the pallidum and motor cortex: PD patients demonstrated relatively elevated phase synchrony with the motor cortex in the beta band and this synchrony was reduced by pallidal DBS. Dystonia patients had greater theta band phase synchrony.

Conclusions

Our results support the hypothesis that specific motor signs of movement disorders are associated with elevated network oscillations in specific frequency bands, and that DBS in movement disorders acts in general by disrupting elevated phase synchrony between basal ganglia output and motor cortex.

539 Predicting Neuropsychiatric Symptoms after Subthalamic Deep Brain Stimulation for Parkinson's Disease Based on the Site of Stimulation

Philip E. Mosley; Terry Coyne; Peter Silburn; Michael Breakspear; Alistair Perry

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus for Parkinson's disease (PD) has been associated with neuropsychiatric symptoms such as impulsivity and hypomania. These symptoms can necessitate psychiatric intervention. However, a comprehensive analysis of neurocognitive and neuropsychiatric outcomes with reference to the site of subthalamic stimulation has not been undertaken.

Methods

We examined 64 patients undertaking subthalamic DBS. Participants were assessed with a battery of neuropsychiatric instruments at baseline and at repeated postoperative intervals. A psychiatrist identified patients with clinically-significant emergent symptoms due to stimulation. The site of the active electrode contact and a simulated volume of activated tissue were evaluated with reference to limbic, associative and motor subregions of the subthalamic nucleus. We studied anatomical correlates of longitudinal neuropsychiatric change and delineated subthalamic regions associated with neuropsychiatric impairment. We tested the ability of these data to predict clinically-significant symptoms.

Results

Subthalamic stimulation within the right associative subregion was associated with inhibitory errors on the Excluded Letter Fluency test at 6-weeks and 13-weeks postoperatively. Subthalamic voxels associated with inhibitory errors were identified in the right associative and motor subregions. At 6-weeks, clinically-significant neuropsychiatric symptoms were associated with the distance of the active contact to the right associative subregion and stimulation within the right associative subregion. At 13-weeks, clinically-significant symptoms were associated with the distance to the right and left associative subregions and stimulation within the right associative subregion. Subthalamic voxels associated with high and low likelihood of postoperative neuropsychiatric symptoms were identified in ventromedial and dorsolateral zones, respectively. A classifier trained on these data predicted clinically-significant symptoms with an accuracy of 79%.

Conclusions

These data underscore the importance of accurate electrode targeting, contact selection and device programming to reduce postoperative neuropsychiatric impairment. The ability to predict neuropsychiatric symptoms based on subthalamic data may permit anticipation and prevention, improving safety and tolerability.

540 A Comparison of Lead Location, Placement Accuracy, and Clinical Outcomes Following Intraoperative MRI- and MER-guided Pallidal Deep Brain Stimulation for Parkinson's Disease

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Introduction

Deep brain stimulation (DBS) lead placement using intraoperative MRI (iMRI) is an alternative surgical technique utilizing real-time intraoperative neuroimaging to guide electrode placement. However, there is limited literature on clinical outcomes with this procedure, especially in comparison with more traditional DBS guided by microelectrode recordings (MER).

Methods

All patients with PD undergoing GPi-DBS between July 2007 and August 2016 with either MER-guidance or iMRI-based targeting using ClearPoint® (MRI Interventions) were retrospectively identified. Measures including lead location and lead placement accuracy, adverse events, pre-operative and 12 month post-operative follow-up DBS UPDRS-III motor scores, levodopa equivalent daily dose, and stimulation parameters were obtained and stratified by surgical procedure.

Results

Seventy-seven patients underwent GPI lead placement with a total of 131 DBS leads. The stereotactic accuracy of the ClearPoint system with respect to lead placement was 1.07 ±0.10 mm, while complication rates were 17.2% vs. 20.8% for MER- and iMRI-guided DBS, respectively. Sixty three patients were included in clinical outcome analyses based on predefined inclusion criteria 20 underwent MER-, and 43 underwent iMRI-guided DBS. The overall improvement in UPDRS-III motor scores was 36.2 ±3.3%, with greater improvement seen following iMRI-guided DBS (43.3 ±3.3%) as compared to MER-guided DBS (20.9 ±6.5%). When only the contralateral hemibody was assessed, the improvement was 46.7 ±3.1% across all patients regardless of procedure performed, or 50.3 ±3.4% and 38.0 ±6.6% for iMRI- and MER-guided DBS groups, respectively. Both groups exhibited similar reductions in LEDD (16.8 and 16.9%, respectively).

Conclusions

The use of iMRI-guided DBS in PD patients was associated with significant improvement in clinical outcomes, which were comparable to previously reported outcomes following MER-guided lead placement in the GPi. However, when we compared this group of patients to a historical cohort of patients treated with MER guided lead placement, we observed greater improvement in motor outcomes following iMRI-guided GPi-DBS.

541 Prefrontal Cortical Implants to Study and Treat Anxiety and Depression in Parkinson's Disease

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Introduction

Depression and anxiety are among the most prominent non-motor symptoms in Parkinson's disease (PD) and the pathophysiology underlying these symptoms remains largely unknown. We used permanent prefrontal cortex implants to investigate neural correlates of these symptoms and to develop a novel neurostimulation therapy for these mood symptoms of PD. This study focused on the orbito-frontal cortex (OFC), part of the cortico-striatal-thalamic circuit that has been implicated in major depression in previous non-invasive studies.

Methods

Two PD patients undergoing DBS surgery for motor fluctuations who also had moderate pre-operative anxiety and depression symptoms were enrolled in this study. In addition to bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) leads, both patients were implanted with a permanent 4-contact ECoG strip with at least 2 contacts covering the right OFC. The ECoG strip and ipsi-lateral DBS lead were attached to an Activa PC+S. Cortical and STN potentials were recorded during regular clinic visits either on or off Parkinsonian medication conditions. Patient1 was instructed to trigger recordings at home, during the presence of minimal and more severe anxiety or depression. Recordings were paired with assessments of mood based on visual analogue scales (VAS). The effect of acute (15min-24hr) OFC stimulation was also studied in patient1.

Results

We found: 1) a peak in the alpha/beta band in the power spectrum of the OFC potentials. 2) Dopaminergic medication did not consistently affect OFC signals, although it did reduce STN beta power. 3) The severity of depression and anxiety was significantly correlated with OFC beta power ($p<0.01$). 4) Acute OFC stimulation (3V, 80-100us, 100-180Hz) was associated with a reduction of these symptoms without inducing side effects.

Conclusions

These preliminary results suggest that OFC beta oscillations may be associated with anxiety and depression in PD, and indicate a potential therapeutic effect of OFC stimulation.

542 Musician's Dystonia Treated with Stereotactic Ventro-oral Thalamotomy

Prajakta Suresh Ghate; Takaomi Taira; Shiro Horisawa

Introduction

Focal hand dystonia in musicians, also called Musician's Dystonia, is a task specific movement disorder, characterized by abnormal twisting or involuntary finger movements and/or postures, manifested only while playing a particular musical instrument. It may lead to music performance career interruption or even termination of job of the affected professional musicians. Majority of the treatments available today are yet to furnish consistent and satisfactory outcome. We present the follow-up results of 64 musician's dystonia patients treated with Ventro-oral thalamotomy.

Methods

64 patients with medically intractable task-specific focal hand dystonia evident only while playing musical instruments and undergoing stereotactic Ventro-oral thalamotomy between October, 2003 and September, 2017 were included in our study. We used the Tubiana scale to evaluate these patients before and after the thalamotomy. The Tubiana scale stages were recorded on subsequent follow-up along with monitoring for adverse events and were statistically analyzed.

Results

Immediate post Ventro-oral thalamotomy improvement of dystonic symptoms was observed in all except 2 patients (96.9%). 4 patients had recurrence or deterioration of dystonic symptoms during follow-up. The mean follow-up duration was 25.1 months. No adverse events were encountered.

Conclusions

This study confirms favorable outcome of musician's dystonia patients treated with Ventro-oral thalamotomy showing excellent improvement in dystonic symptoms, along with preservation of this effect for a considerable duration at follow-up.

543 Neuroprotective Effects of Chronic Opto-chemogenetic Stimulation on Dopaminergic Neurodegeneration Induced by Oxidopamine

Thomas Shiu; Ken Berglund; Alejandra M. Fernandez; Claire-Anne Gutekunst; Robert E. Gross

Introduction

Parkinson's disease (PD) is caused by progressive loss of dopaminergic (DA) neurons in substantia nigra compacta (SNc). Physical exercise is known to alleviate PD symptoms in patients and rodent models, and to induce release of brain-derived neurotrophic factor (BDNF). We hypothesized that directly driving DA neurons would lead to release of BDNF and activation of its Trk B receptor, leading to neuroprotection. To test this hypothesis in a rodent model, we chronically upregulated activity of SNc DA neurons by chemogenetic neuromodulation with luminopsin (LMO), a fusion protein of channelrhodopsin and bioluminescent luciferase. Upon systemic administration of its substrate, coelenterazine (CTZ), the luciferase moiety emits bioluminescence that in turn activates the opsin moiety, enabling sustained excitation non-invasively.

Methods

LMO was expressed in SNc DA neurons via unilateral stereotaxic injection of AAV vectors in Cre-recombinase transgenic mice. To chronically activate LMO, CTZ was given by daily intraperitoneal injection. In some animals, the BDNF-TrkB pathway was blocked by a TrkB antagonist, ANA-12. Shortly after the start of the treatment, unilateral loss of DA neurons was induced by oxidopamine (6-OHDA) injection in the ipsilateral striatum. Ipsiversive circling behavior was assessed before and after the injury once a week up to a month. At the end of experiments, histology was performed to confirm proper LMO targeting to DA neurons as well as to count SNc DA neurons.

Results

Chronic CTZ treatment significantly reduced ipsiversive rotations compared to vehicle-treated control animals. Loss of SNc DA neurons was significantly less severe in CTZ-treated animals, consistent with the behavioral results. ANA-12 diminished these effects of CTZ.

Conclusions

These results support that driving neuronal activity by chronic opto-chemogenetic stimulation of DA neurons provided neuroprotection against 6-OHDA injury and alleviated rotational behavior in a rodent model of PD. Furthermore, the results verify the involvement of the BDNF-TrkB pathway in this neuroprotective effect.

544 Impact of Spinal Cord Stimulation over Anticipatory Postural Adjustment: Possible Key of Mechanism of Gait Improvement Freezing of Gait in Parkinson's Disease

Andrea Cristina de Lima Pardini; Carolina Pinto de Souza; Carolina De Oliveira Souza; Maria Gabriela Dos Santos Ghilardi; Daniel Boari Coelho; Luis Augusto Teixeira; Erich Talamoni Fonoff

Introduction

Gait disturbances and freezing of gait (FoG) are common in late Parkinson's disease (PD), often leading to loss of independence and increasing morbidity. A recent pilot study suggested positive effects of spinal cord stimulation (SCS) in PD patients previously treated with DBS. Despite the encouraging clinical results, no mechanistic approach was investigated at the initial trial. Anticipatory postural adjustment (APA) is an essential aspect of postural control, combines motor and cognitive components of movement preparation and has been thought to be controlled by cortical circuitry. This is shortened during FOG in PD patients.The aim of this study is to evaluate the effects of SCS over the APA measurements in PD patients and its correlation to gait improvement.

Methods

4 PD patients with gait disorder and FoG, previously treated with STN DBS were evaluated in 3 conditions: SCS at 300 Hz, SCS at 60 Hz and SCS turned off. DBS was kept always on. We evaluated the SCS effects on APA and FoG. The biomechanical assessment comprised: 1) Force plate analysis during step initiation measuring the amplitude and time of APA (time between onset of APA and the step); 2) Accelerometry spectral analysis during 10m-walk test providing the percentage of FoG occurrence.

Results

For each patient was calculated the average of 3 trials: 60-OFF/OFF*100 or 300-OFF/OFF*100, which is the gain of the condition (60Hz or 300Hz) in relation to OFF condition. For the group (N=4)a t-test was applied. FoG index was reduced in SCS 300Hz in relation to SCS Off and 60Hz stimulation (p0.042). Patients had significantly less in freezing time while under SCS at 300Hz. APA time decreased in 300Hz condition comparing with OFF and 60 Hz conditions (p0,041).

Conclusions

300 Hz SCS seems to improve gait by decreasing FoG and increasing the efficiency of the preparation and movement coupling during step initiation.

545 Movement-Modulation Of Local Power And Phase Amplitude Coupling In Bilateral Globus Pallidus Interna In Parkinson Disease

Nicholas Au Yong; Mahsa Malekmohammadi; Joni Ricks-Oddie; Nader Pouratian

Introduction

The execution of daily manual tasks involves the coordination of bihemispheric cortical and subcortical motor areas. However, the extent and manner in which bilateral basal ganglia motor networks are coordinated for lateralized movement is unclear. While exaggerated ß (13-35 Hz) power and ß phase-encoded Phase amplitude coupling (PAC) have been implicated in the pathophysiology of Parkinson disease, there is emerging evidence that they also subserve interhemispheric motor processes for coordinating bilateral basal ganglia networks. In this study, we directly compared local beta oscillatory power and beta phase-encoded PAC within bilateral globus pallidus interna (GPi) to identify frequency-specific symmetries and asymmetries that would respectively support interhemispheric coupling and hemispheric lateralization during unilateral movement.

Methods

Bilateral GPi local field potentials (LFP) were recorded simultaneously during rest and cued left hand movement (finger tapping) in nineteen subjects with idiopathic PD, while undergoing awake deep brain stimulation (DBS) implantation. We assessed unilateral movement-related changes to pallidal ß oscillations and ß phase-encoded PAC in comparison to rest.

Results

With unilateral hand movement, high ß (21-35 Hz) oscillations were symmetrically attenuated in bilateral GPi while low ß (13-20 Hz) power was significantly attenuated only in the contralateral GPi (P=0.009, paired t-test). Despite these significant differences, the overall ß spectral profile were largely symmetrical between hemispheres. In comparison, marked asymmetry was observed between bilateral GPi ß phase-encoded PAC during unilateral movement behavior, with significant ß-low gamma (40-80 Hz) PAC attenuation occurring only in the contralateral GPi (P=0.004, Wilcoxon signed-rank test).

Conclusions

These findings indicate that ß oscillatory power and ß phase-encoded PAC subserve distinct motor operations. The high-degree of symmetry between bilateral GPi ß power with unilateral movement is most consistent with global behavior state where as lateralizing ß phase-encoded PAC, reflecting alterations in large-scale effective connectivity, more specifically represents motor behavior.

546 Intraoperative Stimulation of Subthalamic Nucleus During Asleep Surgery Reduces Required Current Threshold for Motor Evoked Potentials

Michael Kogan; David Caldwell; Jeneva Cronin; Brady Houston; Chou-Hung Kuo; Vicente Martinez; Kurt Weaver; Andrew Lin Ko

Introduction
Asleep, image-guided DBS surgery has become standard at many institutions; however, multiple factors affect accuracy of lead placement. Novel placement of subdural electrocorticographic strips also allows for both the recording of motor evoked potential during surgery and programming of closed-loop protocols. We investigate the modulatory influence of STN DBS stimulation on threshold MEP current necessary to drive EMG response.
Methods
Patients scheduled to undergo STN DBS were consented for participation with intraoperative ECoG strip placement and DBS research protocols and intraoperative recording. The Tucker David Technologies (TDT) 5Z5D bioamp processer was used for STN stimulation and ECoG recording. Median nerve SSEP phase reversal methodology identified electrodes over motor cortex. MEPs were then conducted identifying qualitative minimum current (n) threshold to elicit a resultant EMG response. The effect of DBS for each electrode pair (0-/1+,1-/2+,2-/3+) was tested with DBS off (baseline), stimulation (DBS), and off again (washout). DBS conditions were tested with 5 increasing MEP stimulation amplitudes. All data was analyzed using MATLAB software using maximum recorded EMG response. Statistics were calculated using an estimated EC50 approach as well as an n-way ANOVA.
Results
Five Parkinson's patients underwent bilateral, asleep, image-guided STN stimulation with left-sided subdural strip placement at our institution. In four of five patients, the most proximal electrode pairs, 2-/3+, showed the largest decrease in MEP threshold, which was significant with either the EC50 based or ANOVA statistical analyses. In one patient, the greatest effect on threshold was seen in the middle, 1-/2+ electrode pair.
Conclusions
Bipolar DBS stimulation produces consistent effects on MEP thresholds, with the superior electrode pairs having a marked modulatory effect in most patients. These results may reflect increased cortical activity with DBS stimulation at a specific anatomic area and may be useful for intraoperative physiological electrode confirmation in asleep settings.

547 Feasibility of White Matter Trajectory Analysis in Postoperative Diffusion Weighted Images for Patients with Deep Brain Stimulation

Jennifer Muller; Mahdi Alizadeh; Sara Thalheimer; John James Pearce; Victor M. Romo; Shiva Shahrampour; Feroze Mohamed; Ashwini D. Sharan; Chengyuan Wu

Introduction

High frequency deep brain stimulation (DBS) is believed to produce therapeutic effects through modulation of basal ganglia circuits in patients with advanced Parkinson's Disease (PD).[2] Functional connectivity in these and associated circuits have been observed in PD patients.[1] Only within the past ten years have DBS implants become compatible for use with magnetic resonance imaging.[7] This presents the opportunity for the application of advanced imaging techniques such as diffusion weighted imaging (DWI) for imaging after DBS. Clinical application of DWI post-DBS is challenging due to the production of strong susceptibility artifacts.[4] The aim of this study is to use DWI and fractional anisotropy (FA), to identify significant white matter regions unaffected by susceptibility artifact.

Methods

Four patients were included in this study. All subjects underwent pre-and post-operative MRI examinations, which included DWI sequences. AAL, GPi, and STN atlas structures were co-registered to the preoperative DTI using FNIRT. Postoperative FA maps were registered to preoperative the FA map and ROI-based analysis was performed. Outliers were determined by calculating the percent change of FA between scans.

Results

FA increased in the majority of structures for all patients, with some structures showing no change. Three patients had more significant changes in FA within the target basal ganglia; and two had structures affected due to proximity to the site of the extension connector. Most regions demonstrated an average of ~40% change, with outliers exceeding 200% change(Table2).

Conclusion

This study provides impetus towards the integration of postoperative DWI and tractography as a tool for studying regions not been affected by device artifact. Our results demonstrate the ability to image and analyze the majority of brain structures post-DBS using DWI, under predesignated parameters for MRI safety. This data could provide a new baseline from which to measure changes in FA and in relevant brain networks after therapeutic neuromodulation.

548 Long-Term Effects of Endogenous C3 Transferase Expression in Dopamine Secreting Neurons

Rohan Vij Gupta; Claire-Anne Gutekunst; Angel J Santiago-Lopez; Kaavya Mandi; Ken Berglund; Robert E. Gross

Introduction

In Parkinson's disease (PD), the degeneration of dopaminergic neurons of the substantia nigra pars compacta results from the pathological accumulation of alpha-synuclein. Symptoms worsen as these neurons are lost despite dopamine replacement, creating a critical need to develop better neuroprotective therapies. Our approach utilizes gene therapy to introduce C3 transferase (C3), a bacterial exoenzyme that inhibits RhoA, a key intracellular inhibitory GTPase responsible for propagating axon growth collapse and cell death. We hypothesize that long-term endogenous expression of C3 in dopaminergic neurons will not exert major neurotoxic effects, allowing further assessment of its neuroprotective potential in PD.

Methods

We have developed floxed adeno-associated viral (AAV-DIO-Ef1a-GFP-2A-C3) vectors for gene delivery of C3 for long-term expression in the central nervous system (CNS) in a cell-autonomous (endogenous) fashion. These vectors were injected via a unilateral stereotactic injection into the substantia nigra of TH-Cre mice for specific expression in the nigrostriatal pathway. Mice were assessed for behavioral abnormalities by amphetamine-induced rotational analysis and compared to control mice receiving the viral vector without C3 and mice lesioned with 6-hydroxydopamine (6-OHDA). After 28 days, mice were sacrificed for brain sectioning and immunohistochemistry with markers of cell death.

Results

Mice injected with C3 exhibited similar ipsilateral rotations to the site of injection in comparison to control mice and significantly fewer ipsilateral rotations in comparison to mice lesioned with 6-OHDA. Upon sectioning and staining, C3 was expressed endogenously in dopaminergic neurons in a continuous manner with strong expression of tyrosine hydroxylase and weak expression of cleaved activated caspase 3, indicating cell viability and minimal induction of apoptosis.

Conclusions

These findings demonstrate that virally-transfected dopaminergic neurons express C3 without significant neurotoxicity, supporting its safety in long-term endogenous expression. Utilization of gene therapy with C3 should be investigated further as a therapeutic option for patients affected with PD.

549 Optimal STN Targeting and One Year Clinical Outcomes in 159 Patients Treated for Parkinson's Disease using 'Asleep' Robotic Electrode Implantation.

Catherine Moran; Steven Gill; Mariusz Pietrzyk; Carter S. Gerard; Neil Barua; Nagaraja Sarangmat

Introduction

Techniques used to implant DBS electrodes under general anaesthesia without performing micro-electrode recordings have emerged in recent years. We report the largest cohort to date using an 'asleep' method with Robotic guided implantation. Clinical outcome of 159 consecutive patients treated with bilateral STN implantation using the NeuroMateTM Robot was examined. Active contacts of 298 electrodes were mapped to their auto-segmented STN volumes and those producing best clinical improvements were clustered within the STN.

Methods

A retrospective review of patients who underwent surgery between 2012 and 2016 was performed. Robot-guided burr hole drilling created an exact fit for push-fit guide tube insertion. Targeting accuracy was assessed using on-table O-armTM imaging prior to electrode implantation. Clinical outcome was assessed comparing pre-operative off-medication with post-operative off medication on-stimulation scores after one year. We examined the optimal target position by clustering contact points associated with the best clinical outcomes. The STN volumes were normalised using their own geometry.

Results

151 patients underwent follow up. UPDRS III scores improved by 47% (39 to 20.5 points, p<0.001).Total UPDRS, UPDRS II and UPDRS IV scores improved by 46%, 44% and 49% respectively (p,0.001). PDQ-39 self-assessment demonstrated statistically significant improvement in five of the eight sub-scores. Gait, assessed using the Tinetti Assessment Tool (n=135), improved by 19%. Complications included two haemorrhages (no long-term neurological sequelae) and three infections requiring system explantation. Examining optimal contact position, clusters were obtained for those patients who obtained a greater than 70% UPDRS III improvement versus improvement less than 20%. Further clusters were obtained for greater than 70% and less than 20% improvement in specific symptom categories; tremor; rigidity; akinesia; axial and gait.

Conclusions

This method of 'asleep' DBS insertion gives comparable clinical outcomes to other techniques described. Optimised target position using contact clustering within STN for this patient cohort was defined.

550 Delayed Scalp Erosion After DBS Surgery: Incidence, Treatment, Outcomes and Prevention

Justin D. Hilliard; Alberto Bona; Michael S. Okun; Kelly D. Foote

Introduction

Deep brain stimulation (DBS) is an established therapeutic modality for movement disorders, however, complications related to the surgical technique and the implanted hardware do occur and must be minimized to optimize outcomes. Delayed erosion of the scalp overlying protruding DBS hardware is one such adverse event that universally requires surgical treatment and often necessitates explantation of the DBS system. In this study, we evaluated the incidence of delayed scalp erosion in a large single center series of DBS patients, and we propose a surgical strategy for avoiding this complication. We have modified our surgical technique to eliminate protrusion of DBS hardware, effectively preventing delayed erosions. This technique consists of drilling a recess around the burr hole to countersink the DBS cap, and drilling a groove in the parietal calvarium to countersink the connector.

Methods

We performed a retrospective review of 1053 consecutive DBS lead implantations and 867 lead extension cable placements at a single center (UF) by a single surgeon (KDF) from 2002 to 2014. Patients were separated into countersunk and non-countersunk groups based on the surgical technique applied at the time of implantation. We routinely began countersinking the frontal cap in 2011 and the connector in 2013. Each patient had a follow-up time of at least 12 months.

Results

No frontal scalp erosions developed at sites where the cap had been countersunk versus 11 erosions (1.4%) in the non- countersunk group. One parietal scalp erosion developed at the site where the connector had been countersunk versus 12 erosions (1.5%) in the non-countersunk group.

Conclusions

There was a statistically significant reduction in erosion of the frontal DBS cap with countersinking technique and a strong trend toward significant reduction in wound erosion of the lead extension connector. We propose that the countersinking technique should become standard of care due to decrease in wound erosions.

551 Gradient-based Resting fMRI Parcellation for Mapping Functional and Epileptogenic Brain Areas

Ashesh Mehta

Introduction

The cerebral cortex is composed of functional modules that are distinct from pathological modules that are targets for resection in epilepsy surgery. Current invasive electrode protocols are limited by sampling the entirety of these modules. We applied resting functional MRI (fMRI) to parcel brain areas based upon intrinsic functional connectivity (iFC). We used iFC gradients (Wig et al., 2014) to distinguish functionally distinct cortical areas within brains of individual patients (Xu et al., 2016) undergoing epilepsy surgery. We then tested these gradient-based parcellations against clinical identifications of functional and seizure onset zones obtained from invasive monitoring.

Methods

For 3 patients with focal neocortical epilepsy, gradients were derived from iFC similarity and used to define edges for a functional parcellation of brain areas within each subject (Xu et al., 2016). These parcellations were compared directly to functional and epileptogenic brain areas identified in the course of invasive mapping. Areas of function were defined using data from clinical stimulation mapping (CSM) of implanted patient electrodes. For this analysis, assessment of brain function was restricted to language (including speech arrest, picture naming, auditory naming) and motor phenomena. Areas involved in seizure onset were identified using epileptologist review of intracranial electroencephalography.

Results

Gradient-based resting fMRI parcellations corresponded to either a functional or an epileptogenic zone of the brain identified in the course of invasive surgical monitoring for each of the 3 patients studied. In one patient, gradient-based parcellations correspond to edges of the seizure onset zone as defined by invasive monitoring (Figure 1). We find that gradient-based resting fMRI parcellations can identify regions of function and epileptogenic pathology in the brain in this limited sample.

Conclusions

Gradient-based resting fMRI parcellation provides a promising method to identify seizure onset zones as well as functional zones in the brain.

552 Human Spike Recordings Acquired in the Context of an Open-source, Intraoperative Paradigm

Anand Tekriwal; Gidon Felsen; Aviva Abosch; John Thompson

Introduction

Neurosurgical interventions that use active patient feedback, such as the implantation of a deep brain stimulating electrode, create an opportunity to conduct human behavioral experiments during the acquisition of invasive neurophysiology. Here, we present a modular, inexpensive system for auditory decision-making tasks, including stimulus presentation and collection of motor responses. Using our system, we characterize behavioral responses with latency to respond and accuracy of response. In addition, we analyze the temporal pattern of substantia nigra pars reticulata (SNr) spiking relative to specific task events.

Methods

We describe the implementation of an auditory-cued decision-making task designed for use in the intraoperative setting. We have created an auditory-stimulus guided, two-alternative forced choice (2AFC) task using the PsychToolBox suite developed in Matlab. Task responses are collected using an Arduino based single-hand held controller that has been customized with a 3D printed attachment. Neural activity is recorded from microelectrodes via an NeuroOmega system (Alpha Omega, Alpharetta GA). Task and neural data are aligned according to TTL signals sent from DATAPixx (VPixx Technologies, Montreal, Quebec), triggered by Matlab.

Results

We demonstrate the utility of a simple-to-implement sensory-motor task amenable to an intraoperative setting that can be combined with invasive neurophysiology. Data collected and analyzed to date demonstrates that single-unit activity reflects task variables associated with our 2AFC. Specifically, analysis of two putative SNr neurons show significantly ($p<0.05$, non-paired t-test) increased firing rate prior to movement execution, in comparison to firing rate following movement execution.

Conclusions

For very low cost and minimal effort, most clinical neural recording system can be adapted for concurrent intraoperative behavioral testing using our framework. Barriers to conducting intraoperative electrophysiological studies in awake behaving human subjects remain high, but our work should significantly decrease the effort needed to implement a system with rich recording capabilities.

553 Differences in Cortical Oscillations During Self-initiated Movement Between Parkinson's Disease and Essential Tremor

Jeong Woo Choi; Mahsa Malekmohammadi; Zhang Xu; Justin Sharim; William Speier; Nicholas Au Yong; Nader Pouratian

Introduction
Patients with Parkinson disease (PD) express difficulty in initiating movements, particularly for those movements that are self-initiated (SI). These deficits are primarily associated with the rigidity and bradykinesia and have been linked to the beta (13-35 Hz) hypersynchrony within the basal ganglia thalamocortical network. While previous studies provided important insight, dynamics of cortical activity during the SI movement and how they relate to the disease symptoms remain relatively underexplored. Here, we explore the dynamics of movement-related cortical oscillatory activity in subjects with PD or essential tremor (ET).

Methods
Sensorimotor cortical electrocorticogphy signals were recorded from 13 PD and 10 ET patients during awake intraoperative implantation of deep brain stimulation lead. Each subject performed two blocks of externally cued (EC) or SI finger tapping task of the contralateral hand. We assessed movement-related changes in local spectral power of the cortical signals during the period of movement initiation, and statistically compared those between two disease groups for each movement type.

Results
For SI trials, movement related suppression of beta power and broadband gamma (70-200 Hz) increase, started earlier in PD compared to ET patients at motor/pre-motor cortices ($p=0.007$ for beta power, $p=0.01$ for gamma power, Wilcoxon rank-sum test). On the contrary, there was no significant difference in this timing between two disease groups during the EC trials. During SI movements, the magnitude of beta power suppression and gamma power increase at the sensory cortex was positively correlated with the severity of rigidity and bradykinesia in PD cohort ($p=0.004$ for beta power, $p=0.007$ for gamma power, Spearman correlation).

Conclusions
Our findings show disease specific patterns of movement related power change at the motor cortex and provide new evidence that rigidity and bradykinesia in PD are associated with an earlier and stronger movement related power change at the motor cortex when subjects are performing a SI movement.

554 Involvement of Nigrofugal Fibers and Correlation with Clinical Outcome in STN-DBS for Parkinson's Disease

Josue Moises Avecillas-Chasin; Christopher Honey

Introduction

Deep brain stimulation of the subthalamic nucleus (STN) is an effective therapy for patients with Parkinson's disease (PD). Different regions within the subthalamic area have been correlated with optimal clinical outcomes and undesired side effects. In this work, we correlate the motor outcome in PD patients with the degree of nigrofugal fiber stimulation.

Methods

Thirty-five patients with STN-DBS were included and their clinical and stimulation parameters were recorded at one-year follow-up. The volume of activated tissue (VAT) for all patients was modelled using finite element method within the Lead-DBS software. All VATs were summed and analyzed using generalized linear models in FSL software to obtain statistically significant stimulation clusters (StimC) correlated with: greater reduction of dopaminergic medication, improvement in Unified Parkinson's Disease Rating Scale (UPDRS) III, bradykinesia, and rigidity scores. Nigrofugal pathways (nigroputaminal and nigropallidal) were obtained using probabilistic tractography with imaging data from 35 PD matched subjects from the Parkinson's Progression Markers Initiative connectome. Finally, we calculated the overlap of StimC with the nigrofugal fibers and STN.

Results

Significant reduction of symptoms was obtained with STN-DBS in our patients ($p<.05$). Nigroputaminal and nigropallidal pathways were traced as described in previous anatomical descriptions. StimC with the greatest dopaminergic medication reduction overlapped with the nigroputaminal fibers (coeff0.50) and not with the STN. StimC with the greatest UPDRS improvement showed more overlap with nigroputaminal and nigropallidal pathways (coeff0.49,0.38) than the STN (coeff0.05). Two StimC with greater bradykinesia improvement overlapped with the nigropallidal fibers (coeff0.55) and the STN (coeff0.19). Finally, two distinct StimC correlated with greater rigidity improvement overlapped with nigroputaminal fibers (coeff0.30) and the STN (coeff0.26).

Conclusions

Electrical field involvement of the nigroputaminal fibers, more than the STN, appears to produce the most improvement in UPDRS III, rigidity, and reduction of dopaminergic medications. Similarly, nigropallidal fibers involvement is associated with greater bradykinesia improvement.

555 Outcomes of a Prospective, Multicenter International Registry of Deep Brain Stimulation

Jan Vesper; Roshini Jain; Heleen Scholtes; Alex Wang; Steffen Paschen; Michael T. Barbe; Andrea Kühn; Monica Pötter-Nerger; Jens Volkmann; Günther Deuschl

Introduction

The effectiveness of Deep Brain Stimulation (DBS) for reducing motor complications of PD has been substantiated by randomized controlled trials (Schuepbach et al.,2013). Additionally, motor improvement is sustained for up to 10 years (Deuschl et al. 2013). Large patient data registries may facilitate insights regarding real-world, clinical use of DBS. Furthermore, no registry database currently exists for a multiple-source, constant current DBS system.

Methods

The Vercise DBS Registry is a prospective, on-label, multi-center, international registry sponsored by Boston Scientific Corporation. The Vercise DBS system (Boston Scientific) is a multiple-source, constant-current system. Subjects were followed up to 3 years post-implantation where their overall improvement in quality of life and PD motor symptoms was evaluated. Clinical endpoints evaluated at baseline and during study follow included Unified Parkinson's disease Rating Scale (UPDRS), MDS-UPDRS, Parkinson's disease Questionnaire (PDQ-39), and Global Impression of Change.

Results

To date, 290 patients have been enrolled in the registry and this report will provide an overview of the data collected so far from implanted patients within this cohort. At 1 year post-implant, 36.2% improvement in MDSUPDRS III scores (stim on/meds off) compared with baseline was reported. This improvement in motor function was supported by an improvement in quality of life as assessed by PDQ39 Summary Index (5.6 point improvement, n = 146) at 1 year. Roughly 90% of patients and clinicians reported improvement as compared with Baseline.

Conclusions

This DBS registry represents the first comprehensive, large scale collection of real-world outcomes and evaluation of safety and effectiveness of a multiple-source, constant-current DBS system.

556 Technical Considerations for Surgical Targeting of the Substantia Nigra

John Lamm; George Quintero; Greg A. Gerhardt; Craig Gilmour van Horne

Introduction

The subatantia nigra has recently gained traction as a target for deep brain stimulation (DBS) in clinical trials for Parkinsonian gait improvement as well as gene therapy delivery and cell therapy strategies in Parkinson's Disease (PD). The potential electrophysiologic variability of the substantia nigra due to its inherent heterogeneity and its potential alteration in PD progression have made mapping throughout the nucleus more difficult and less defined than other basal ganglia nuclei. We report our experience in PD study participants with peripheral nerve grafts targeting the substantia nigra using visual based targeting both with and without microelectrode recording (MER).

Methods

Thirty participants were included in our study with a total of 47 different peripheral nerve graft implantations into the substantia nigra. Each participant underwent a pre-operative 3T MRI which was imported into Brainlab for definition of the substantia nigra structure, target determination using SWI and T2 sequences, and trajectory planning using T1 with contrast and T2 sequences. Participants underwent nerve graft implantation at the time of DBS lead implantation using of a CRW headframe. Intraoperative MER was used to aid in confirming 18 of the 47 targets intraoperatively.

Results

Post-operative MRI review and trajectory mapping after 47 peripheral nerve graft implantations within the substantia nigra demonstrated no occurrences of graft material or delivery cannula tract termination outside of the substantia nigra. Accuracy was not significantly impacted by the use of MER. Side effect profiles with graft implantation were not significantly different from DBS alone. Early data shows promising improvements in UPDRS part III scores but is still being collected.

Conclusions

Visual based targeting is a safe and accurate method for the purpose of intranigral targeting for therapeutic trial delivery in PD. MER can be used to identify the nigral-STN border, but may not provide additional benefit in all intranigral targeting applications.

557 Developing a Comprehensive Quality Improvement Registry for DBS in Parkinson's Disease

James McInerney; Joohi Jimenez-Shahed; Elana Farace; Rachel Saunders-Pullman; Jason M. Schwalb; Ludy Shih; Elena Moro; Michelle York; Susan Bressman; Michelle Burak; James Kirk; Meredith Spindler

Introduction

Considerable evidence favors deep brain stimulation (DBS) over best medical management when motor complications are present in Parkinson's disease (PD) patients. Nevertheless, variability in outcomes are not well understood, best practices are not well defined, and prospective, long-term health economics data and comparisons of treatment techniques are lacking. Randomized trials are impractical to investigate these questions. A DBS registry would effectively address these issues. A large and heterogeneous PD cohort undergoing DBS could be prospectively and comprehensively characterized using standard assessment batteries and image analysis in a quality improvement effort.

Methods

A survey of potential clinical sites investigated which clinical data are routinely captured in the work up of candidates for DBS. Clinician-measured and patient-reported outcomes and imaging studies typically gathered from active movement disorder centers were identified.

Results

Across 25 responding sites, 96% completed a Movement Disorder Society- Uniform Parkinson's Disease Rating Scale (MDS-UPDRS) part III, 70-77% completed MDS-UPDRS parts I, II and IV, 91% completed Hoehn and Yahr staging, and 85% completed a Montreal Cognitive Assessment (MoCA) prior to surgery. The majority do not systematically assess non-motor symptoms or impulse control disorders, and only 68% capture the Parkinson Disease Questionnaire (PDQ-39). No respondents routinely assessed operative risk or patient satisfaction.

Conclusions

This survey identified a comprehensive set of data elements that would be logistically reasonable to capture systematically and benchmark for analysis in a multi-institutional registry. Prospectively capturing standard and comprehensive assessments and analyzing that data in a large PD cohort undergoing DBS, would identify potential changes in therapeutic strategies that could be implemented and analyzed. This data would have broad applicability to a range of practice scenarios and patient characteristics and ultimately improve the quality of DBS care and outcomes for PD patients. The infrastructure of the registry could also be applied to other disease states.

558 In Vivo Characterization of Cortical Activy Elicited by STN DBS During the Acute Response to Electrode Implantation

Aaron J. Suminski; Sara Saleh; Rayan Alkashgari; Joseph Novello; Sarah Brodnick; Jane Pisaniello; Aaron Dingle; Justin C. Williams; Wendell Bradley Lake

Introduction

Deep brain stimulation (DBS) is an established adjunctive method of alleviating symptoms for various movement disorders including Parkinson's Disease (PD). Despite intraoperative testing for optimal placement and efficacy of the stimulating electrodes, optimization of the stimulation parameters to effectively treat the symptoms of PD is a months-long process for many patients. Programming period length may be due, in part, to the inflammatory response to electrode implantation.

Methods

To investigate the effect of inflammation on current delivery, transgenic mice, expressing Thy1-GCaMP6f were anesthesized with isoflurane (5% induction, 2% maintenance) and implanted with a unilateral, concentric DBS electrode (125um diameter) in the subthalamic nucleus (STN) using stereotaxy (-1.7mm AP, -1.5mm ML, -4.5mm DV from bregma). After the surgical procedure, anesthesia was switched to a ketamine (25-100mg/kg)/dexmedetomidine(0.05-0.1mg) cocktail as isoflurane depresses cortical activity. Next, high frequency electrical stimulation of the STN was performed using trains of 10 biphasic pulses (cathodal-first, 100-200 uA; 100us per phase, 150Hz) initiated at pseudorandom intervals. We imaged changes in fluorescence (10Hz frame rate) elicited by stimulation to characterize the response of cortical neurons to STN DBS.

Results

In response to DBS, we observed a widespread wave of depolarization on the cortical surface caused by two separate mechanisms. First, we saw robust activation of the motor areas due to excitation of projections from STN to the cortex. Second, neural activity emanated and then from the site where the electrode entered the parenchyma and decreased with distance from that site.

Conclusions

This result is consistent with the idea that the acute inflammatory response during the perioperative and early postoperative periods shunt current away from the desired target compared to the chronic inflammatory state weeks later. Further understanding the local parenchymal effects of lead implantation will help in the development of methods to reduce the inflammatory response during this process.

559 Primary Cell Battery Longevity in DBS: Results from the Product Surveillance Registry

Peter Konrad; Steven M. Falowski; Keisha Sandberg; Gayle Johnson; Todd W. Weaver

Introduction

Deep Brain Stimulation (DBS) is an effective and well-established treatment for Parkinson's disease (PD), and essential tremor (ET), and dystonia. DBS is powered by an implantable pulse generator (IPG) and battery longevity varies by factors such as the number and types of system components, as well as changes in power demands over the patient and therapy life cycle. Additionally, battery longevity is often not analyzed using survival techniques, which may underestimate battery longevity (ref1). With the increased applications of DBS, the longevity of an IPG is an important factor to patients, caregivers, and physicians. With these key factors considered, this analysis was conducted to assess the battery life in patients who underwent DBS for PD and ET in a real-world registry.

Methods

The Product Surveillance Registry (PSR) is a prospective, long-term, multi-center global registry for DBS to monitor the reliability and safety of Medtronic DBS systems. Patients included in this analysis were treated with DBS for PD or ET. Data from 1250 patients* with 1445 Activa PC IPGs were analyzed using Kaplan-Meier and Cox proportional Hazard analyses. IPGs were excluded from the analysis if adaptors (n =160) were used.

Results

For PD patients, median estimate of battery longevity was 4.6 years for first-time implanted IPGs and 3.7 years for replacement IPGs. The median battery longevity for ET patients was 4.3 years for first-time implanted IPGs compared to 3.9 years for replacement IPGs (Table 1). The 3.5-year survival rate for first-time implanted IPGs was 80.4% for PD patients and 69.6% for ET patients (Figure 1).

Conclusions

This analysis demonstrated the expected performance of 3-5 years of battery longevity for DBS therapy from real-world data collected across diverse settings. Battery longevity is quite similar in PD and ET DBS patients but shorter in replacement IPGs compared to first-time implanted IPGs. While the device model is the same for the first-time implanted versus replacement IPGs, the shorter longevity may reflect either programming changes utilizing more power in replacement devices, or a change in electrical resistance over time (higher tissue impedance resulting in more power consumption for a given programmed setting over the life of the patient).

560 Longer Beta Oscillatory Episodes Reliably Identify Pathological Subthalamic Activity in Parkinsonism

Zvi Israel; Hagai Bergman; Marc Deffains

Introduction

The efficacy of deep brain stimulation (DBS), primarily of the subthalamic nucleus (STN) for advanced Parkinson's disease is often attributed to the suppression of pathological synchronous ß oscillations along the cortico-thalamo-basal ganglia (BG) network. Conventional high-frequency DBS continuously and indiscriminately influences both pathological and normal neural activity. The DBS protocol might be more effective and efficient if stimulation was only applied when necessary (closed-loop adaptive DBS). Our study aimed to identify a reliable biomarker of the current parkinsonian state that could be used as a trigger for adaptive DBS.

Methods

We examined the synchrony and oscillatory features of paired spiking activities recorded in three distinct nodes of the BG network of two African green monkeys before and after induction of parkinsonism (via 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) intoxication).

Results

Spectral and time-domain analysis revealed that parkinsonism-related BG ß synchrony consisted of synchronized time-limited episodes, rather than a continuous stretch of ß oscillatory activity. Moreover, episodic BG ß oscillatory activity, albeit prolonged in parkinsonism, was not necessarily pathological, as short ß episodes could also be detected in the healthy state. Importantly, prolongation of the BG ß episodes was more significant than their intensity in the parkinsonian state - especially in the STN.

Conclusions

Prolonged STN ß episodes are a reliable biomarker for parkinsonism and might be used as an optimal trigger for future adaptive DBS applications.

561 RNA-seq and Histological Characterization of Human Peripheral Nerve Tissue for Use in Brain Grafts for the Treatment of Parkinson's Disease

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Introduction
Currently two clinical trials (NCT01833364 and NCT02369003) are underway which feature the implantation of a peripheral nerve autograft to the brain (targeted to the Substantia Nigra) in combination with Deep Brain Stimulation (DBS) for the treatment of patients with Parkinson's disease. As of 1/8/2018, 46 patients have received a graft. This nerve tissue is harvested from the sural nerve, a cutaneous sensory nerve located in the lateral ankle, from patients undergoing DBS surgery. The tissue receives a conditioning injury in situ two weeks prior to grafting. This study aims to characterize the effect of this conditioning, as well as the state of the nerve graft tissue immediately prior to implantation.

Methods
Two sural nerve tissue samples (pre-conditioned and post-conditioned) per patient were collected from six patients during DBS surgeries 14 days apart. RNA sequencing (RNA-seq) was used to measure absolute and relative levels of gene transcripts in the pre-conditioned and post-conditioned nerve tissue. These findings were supplemented by histology of the nerve tissue.

Results
The results of these experiments show: 1) Consistent similarity within the pre-conditioned and post-conditioned group transcriptomes 2) Consistent changes between the pre-conditioned and post-conditioned group transcriptomes 3) Increased transcript levels related to nerve repair, growth factor production, and immune cell migration pathways 4) Decreased transcript levels related to myelin production pathways, consistent with the repair Schwann cell phenotype. All results are statistically significant ($p < 0.05$).

Conclusions
These findings suggest that the nerve graft tissue implanted in human patients has a pro-regenerative phenotype which has the potential to alter the course of neurodegeneration in the brain.

562 Hospital Resource Utilization with Intraoperative CT for Deep Brain Stimulation Surgery – Preliminary Experience from a Single Center

Nader Delavari; Marian Michael Bercu; Alon Y. Mogilner

Introduction

The use of intraoperative CT (iCT) for DBS provides a number of putative advantages over the traditional radiology suite method, including immediate verification of lead placement as well as increased patient comfort. We present our DBS time data comparing intraoperative CT with the traditional method (standard CT or sCT).

Methods

OR time data from a consecutive series of 58 DBS surgeries utilizing either iCT, (Brainlab Airo, n=29), or sCT with patient transport (n=29) were compared. All cases were done using frame-based CT fused with previously obtained MR imaging, under conscious sedation with microelectrode recording and macrostimulation. Frames were placed in the OR prior to CT with intravenous sedation. In iCT cases, postoperative CT imaging was obtained immediately in the OR following headframe removal. In sCT cases, CT scans were done within the first six hours postoperatively.

Results

The mean total OR time was 179 minutes for the sCT group vs. 199 minutes for the iCT group ($p<0.005$, t-test). Surgical time from skin incision until frame removal was 165 minutes in sCT cases and 171 minutes in the iCT group ($p=0.26$). Mean time between frame removal and iCT completion was 14 minutes. Average transportation time to and from CT in sCT cases was 15 minutes.

Conclusions

Our early experience suggests that while the use of iCT adds approximately 20 minutes to the total OR time, the increase in time is primarily due to the additional postoperative CT not obtained in sCT cases. The additional OR time and cost must be weighed against the additional resources necessary to transport the patient to and from CT scan, and the additional advantages of direct intraoperative target verification, including but not limited to the ability to perform DBS under general anesthesia.

563 An Analysis of Stereotactic Targeting Accuracy and Factors Associated with Increased Rates of Target Radial and Euclidean Error

Christian M. Hoelscher; Richard Frank Schmidt; Ashwini Dayal Sharan; Eiwin Tham; Chengyuan Wu

Introduction

Stereotactic procedures, both neuromodulatory and ablative, depend on a high degree of accuracy to deliver clinical results in a safe and predictable manner. Understanding not only typical margins of error, but also mechanisms of error, will allow for a greater understanding of how to limit surgical inaccuracy during stereotactic procedures.

Methods

We reviewed our most recent laser interstitial thermal therapy (LiTT) and deep brain stimulation (DBS) cases. Stereotactic planning was reviewed and compared against ultimate electrode placement, allowing for calculation of radial and Euclidean errors. All DBS cases were performed asleep with 2 mm burr holes. A variety of patient and procedure-related parameters were reviewed for their correlation with inaccuracy in lead placement.

Results

We reviewed a total of 59 trajectories. There were 13 LiTT cases involving 15 trajectories and 23 DBS cases covering 44 trajectories. Trajectories with < 2mm of target radial error (TRE, n=43) had drill angles that were more orthogonal to the skull (mean 70.2°, with orthogonal taken as 90°) compared to those with > 2mm of TRE (n=16, mean 61.9°, p=0.011). TRE < 2mm was associated with a 13.5% rate of outer skull table electrode deviation or "drill skive", compared to 42.8% for trajectories with TRE > 2 mm (p=0.011). Trajectories with < 2mm of target Euclidean error (TEE, n = 23) had drill angles that were more orthogonal to the skull (mean 70.5°) compared to those with > 2 mm TEE (mean 65.7°, n=28, p=0.018). TEE < 2mm was associated with an 8.3% rate of outer table deviation, compared to 33% for trajectories with TEE > 2 mm (p=0.016).

Conclusions

Maintaining a drill angle as close to orthogonal to the skull as possible is helpful in limiting outer table electrode deviations and the associated degree of target radial and Euclidean error.

564 Propofol Anesthesia Precludes Local Field Potential-based Functional Mapping of Pallidum During DBS Implantation

Hiro Sparks; Mahsa Malekmohammadi; Nicholas Au Yong; Andrew E. Hudson; Nader Pouratian

Introduction

Intraoperative neurophysiology, including microelectrode recording (MER) and micro- and macroelectrode stimulation testing is often used to provide functional confirmation of optimal deep brain stimulator (DBS) lead implantation [1]. While several groups have reported the ability to perform MER under certain anesthetized conditions, it is well accepted that anesthesia can affect MER signals [2]. Given increased interest in the potential role of local field potentials (LFP) for functional mapping and localization, it is important to investigate the potential effects of anesthesia on LFPs recorded during DBS implantation surgery. We aimed to characterize the effect of propofol GA on globus pallidus internus (GPi) and globus pallidus externus (GPe) LFP in Parkinson disease (PD) patients in order to draw conclusions regarding the utility of macroelectrode recordings for lead targeting in the anesthetized patient.

Methods

We recorded LFP from bilateral pallidum in twelve PD patients (i.e. 24 hemispheres) undergoing DBS implantation surgery targeting GPi, while subjects were awake (off anesthesia for at least 1 hour) with eyes open and after propofol-induced loss of consciousness. We used the modified observer's assessment of alertness/sedation scale to evaluate the level of alertness. Recording data was band pass filtered at 1-300 Hz using a 6th order Butterworth IIR filter. Power spectral density was calculated using Thomson's multitaper method in 1 second consecutive time windows.

Results

Propofol administration resulted in a general power shift from high to low frequencies across pallidal signals. Prior to anesthesia, beta power was significantly greater in the GPi compared to the GPe (One-way ANOVA, $P=0.003$). Similar analysis however revealed no significant difference in beta band across the pallidum under propofol anesthesia (One-way ANOVA, $F=0.178$, $P=0.84$).

Conclusions

While GPi and GPe are distinguishable using LFP spectral profiles in the awake condition, propofol anesthesia causes loss of spectral differentiation between GPi and GPe. Therefore, LFP spectra cannot be relied upon in the propofol-anesthetized state for functional mapping and localization during DBS implantation.

565 Intraoperative Monitoring of Dynamic Phase-amplitude Coupling in Motor Cortex in Parkinson's Disease Patients

Yousef Salimpour; Kelly A. Mills; William S. Anderson

Introduction

Phase-amplitude coupling (PAC) reflects the coupling of the phase of oscillations in a specific lower frequency band to the amplitude of oscillations in another higher frequency band. PAC synchronizes populations of neurons within and between brain regions and PAC with various low frequency bands have been associated with working memory in the hippocampus or motor control in the posterior frontal lobe. Differences in PAC between patients and controls have been reported in schizophrenia, Alzheimer disease (AD), epilepsy, and Parkinson's disease (PD). In PD, excessive coupling has been demonstrated compared with non-PD patients, and reductions in PAC are associated with symptom improvement following in PD patients and the association of effective treatments such as dopaminergic deep brain stimulation (DBS) of the subthalamic nucleus. This evidence supports PAC as a potential biomarker for monitoring the efficacy of PD treatments. However, several technological challenges should be addressed before making it available for clinical applications.

Methods

In awake patients undergoing DBS surgery for Parkinson's disease, we used electocorticography (ECoG) signals recorded from motor cortex to monitor time dependent PAC levels. A sliding time window is used and the modulation index (MI) method employed to measure the average MI. By fixing the phase of the low frequency rhythms within the beta band, the temporal development of coupling across the high frequency oscillation is illustrated.

Results

Using electocorticography data recorded intraoperatively in PD patients during deep brain stimulation surgery, we were able to detect PAC between the phase of the beta rhythm and the amplitude of gamma oscillations and track it with a determined delay.

Conclusions

We established a method and system for PAC detection and monitoring with respect to time for PD patients during DBS implantation surgery. This is a preliminary step toward using PAC as a biomarker for real-time monitoring of therapeutic efficacy and may allow for physiology-controlled neuromodulation.

566 Deep Brain Stimulation in Young Children: Technical Challenges and Long-term Assessment of Lead Location

Faisal Al Otaibi

Introduction
Deep brain stimulation (DBS) is a well-established treatment method for certain movement disorders. To date there is less data in the current literature that explore DBS lead location over long term follow up.
Methods
A retrospective analysis of a group of patients who underwent DBS for different types of movement disorders was carried out between the period of January 2011 and June 2016. The DBS was implanted for all patients utilizing standardized surgical techniques and intraoperative neurophysiological monitoring under general anesthesia. The outcome was assessed using the Burke-Fahn-Marsden Dystonia Rating Scale movement subscore (BFMDRS-M). Follow up assessment of the lead location within the target were done using CT brain and electrodes stimulation induced side effects distance measurement.
Results
A total of 16 consecutive young children (females 6, males 8) underwent DBS implantation for secondary dystonia (No. 10), primary dystonia (No.1), chorea (No.1), choreoathetosis (No. 3), and Woodhouse-Sakati Syndrome (No.1). The age was ranging between 5 and 13 years old (mean 8.2 years). The follow up period was ranging between 7 and 38 months. Postoperative improvement was 30-60% using BFMDRS-M in secondary dystonia, 80% in primary dystonia, 40-70% in choreoathetosis and chorea, and 50% in Woodhouse -Sakati syndrome. DBS was implanted in different targets that include GPI, zona incerta, and thalamus. Multitargeting method was used in 4 patients. One patient developed infection, which was treated with unilateral partial system removal and antibiotics and one patient developed Twiddler syndrome that required distal system revision. No lead upward migration from the targets was seen over, 3, 4, and 5 years follow up.
Conclusions
This study showed that DBS improves functional state in various types of movement disorders in young children below that age of 14 years. The best response to DBS was seen in primary dystonia and chorea. No lead migration overtime has been identified.

567 DBS for Pantothenate Kinase Associated Neurodegeneration: A Systematic Review of 100 Cases

Philippe De Vloo; Darrin J. Lee; Robert Dallapiazza; Mojgan Hodaie; Suneil Kumar Kalia; Andres M. Lozano

Introduction

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive disorder, characterized by progressive iron accumulation affecting especially the pallidum and SNr. Since 2001, DBS targeting GPi or alternatively STN or the motor thalamus has been attempted.

Methods

Our systematic review of the literature encompasses 100 cases of DBS for PKAN (58 classic, 14 atypical, 28 unknown).

Results

Despite being affected by iron accumulation, neuronal degeneration and gliosis, GPi was by far the most common target (88/100). Patients with classic PKAN underwent DBS implantation surgery at the median age of 11 years (range 6-34) after a median disease duration of 7 years. 10/58 classic PKAN cases underwent emergent DBS implantation during a dystonic storm. Atypical PKAN cases were operated at a median age of 31 years (range 17-46), after a median disease duration of 15 years. The mean BFMDRS-M reduction after 1 year was 26% but was more prominent in atypical (45%) than in classic (16%) PKAN cases. The response rate (?30% dystonia improvement at 1 year) was 35% in classic and 73% in atypical PKAN. Preoperative dystonia severity, disease duration, proportion of life lived with symptoms, and fixed skeletal deformities and/or muscle contractures were not predictive of outcome. GPi-DBS slightly improved functional disability (BFMDRS-D -13%), and may have improved pain, cognitive scores and quality of life at 1 year postoperatively. After 4-7 years, this improvement was lost, although the relative contribution of disease progression and loss of DBS effect is unknown. The rate of infection and hardware complications was in line with other types of dystonia. However, 2/100 patients died within 3 months and the complication rate was particularly high in patients operated during a dystonic storm.

Conclusions

There is level III evidence that GPi-DBS can reduce dystonia and improve functionality in PKAN, especially in atypical cases.

568 Two Year Outcome of Magnetic Resonance Guided Focused Ultrasound Treatment for Essential Tremor

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Introduction

Magnetic resonance guided focused ultrasound (MRgFUS) is a non-invasive procedure that has recently been investigated as a new treatment modality for essential tremor (ET). Although an initial report demonstrated ~50% reduction in tremor at one year(1), the long-term durability of the procedure has not yet been evaluated. This study reports results at a 2- year follow-up after MRgFUS thalamotomy for ET.

Methods

A total of 76 patients with moderate-to-severe ET, who had not responded to at least two medications, were enrolled in the original randomized study of unilateral MRgFUS thalamotomy and evaluated using the clinical rating scale for tremor. Sixty-seven of the patients continued in the open-label extension phase of the study with monitoring for 2 years. Nine patients did not continue to the two year endpoint. All patients remaining in the study at each follow-up period were analyzed for improvement in tremor persistent adverse effects.

Results

Mean hand tremor score at baseline (19.8±4.9, 76 patients) improved by 55% at 6 months (8.6±4.5, 75 patients). The improvement in tremor score from baseline was durable at 1 year (53%, 8.9±4.8, 70 patients) and at 2 years (56%, 8.8±5.0, 67 patients). Similarly, the disability score at baseline (16.4±4.5, 76 patients) improved by 64% at 6 months (5.4±4.7, 75 patients). This improvement was also sustained at 1 year (5.4±5.3, 70 patients) and at 2 years (6.5±5.0, 67 patients). Paresthesiae and gait disturbances were the most common adverse effects at 1 year-each observed in 10 patients, with an additional 5 patients experiencing neurological adverse effects. None of the adverse events worsened over the period of follow up and 2 of these resolved. There were no new delayed complications at 2 years.

Conclusions

Improvement in tremor after MRgFUS thalamotomy for ET is stably maintained at 2 years. Latent or delayed complications do not develop after treatment.

569 Intracranial Hemorrhage Rates Following MER and iMRI Guided Deep Brain Stimulation Surgery

Prince Antwi; Abhijeet Gummadavelli; Jason L. Gerrard

Introduction

Targeting in DBS surgery is performed by microelectrode recordings (MER) or intraoperative magnetic resonance imaging (iMRI). A reported benefit to iMRI technique is decreased risk of intracranial hemorrhage (ICH), however, these comparisons are typically done with historical data. We hypothesize that the ICH rate in MER-guided DBS surgery would improve over time due to improved safety of MER. ICH rates following MER-guided DBS surgery range from 7-8% in the 1990s to 3.1-3.3% in the early 2000s and 0-2.8% more recently. We report on ICH following DBS surgery for movement disorders at our institution, comparing targeting techniques and microelectrodes as our institution changed electrodes in 2013.

Methods

We performed a retrospective chart review of patients undergoing DBS surgery for Parkinson's disease and essential tremor at our institution between January 2005 and November 2017. All but one patient had imaging (either CT or MRI) within 24 hours after surgery. Hemorrhages were classified as intraventricular, intraparenchymal, or subarachnoid.

Results

We reviewed 208 DBS leads (MER: 161, iMRI: 47) implanted in 124 patients within the study period. Three electrode implantations resulted in asymptomatic intracranial hemorrhages (two subarachnoid and one intraventricular); no symptomatic hemorrhage was observed. Of the three, only the patient with intraventricular hemorrhage had a history of hypertension. Overall hemorrhage rate was 1.44% per lead. On average, 2.11 microelectrode passes were made in MER-guided procedures since 2013. Hemorrhage rate with MER was comparable to that for iMRI (1.86% vs. 0%, p-value = 0.35). Hemorrhage rates were similar between targets (GPI: 3.23%, STN: 1.48%; p-value = 0.51) and between year groups (2005-2012: 2.5%, 2013-2017: 1.19%; p-value = 0.53).

Conclusions

In our cohort, ICH rate following DBS surgery was 1.44%, which compares favorably to historical data and is consistent with our hypothesis of improved MER safety over time. This rate was comparable to that for iMRI-guided DBS.

570 Histological Evaluation of Neuroinflammation Near a DBS Electrode Implanted for 16 Years

Jasmine Singh; Cristin Welle

Introduction

Deep brain stimulation (DBS) is a technique used to treat medically-intractable neurological diseases in humans including Essential Tremor and Parkinson's Disease. However, examination of the effects of chronic implantation of DBS electrodes in the brain is limited to a small number of postmortem samples, typically from patients who were implanted for several years.

Methods

In this study, we have utilized techniques in CLARITY tissue clearing and immunohistochemistry to evaluate the neurological immune response presented in post mortem human tissue from patients that underwent DBS treatment for up to 16 years. Tissue along the extent of the electrode track, including cortical, striatal, and subthalamic nucleus targets were assessed for markers of neuroinflammation and neurodegeneration

Results

In cortical tissue, we observe an increase in microglial and macrophage engulfment of lysosomal debris at the along the DBS electrode track, as indicated by the co-localization of IBA1 positive cells and CD68 positive lysosomal vesicles. In addition, hypertrophic astrocytes also demonstrate phagocytic activity, with evidence of association with local neurodegeneration.

Conclusions

We see evidence of greater neuroinflammation near the electrode track in patient with 16 years of DBS implantation. Future directions for this work include assessing tissues for evidence of neuroprotective markers potentiated by long-term deep brain stimulation.

571 Incidence of Fractures and Migrations of Deep Brain Stimulating Electrode Leads and Connectors: A Single Center Retrospective Review

Elsa V. Arocho-Quinones; Peter A. Pahapill

Introduction

Hardware-related complications in deep brain stimulation (DBS) including fractures, migrations, malfunctions, and skin erosions carry a high morbidity. Reported strategies to mitigate these complications include lead tethering and bone contouring [1-5]. Herein, we report our experience with these cases and compare the incidence of hardware-related complications before and after implementing a simple lead connector anchoring technique.

Methods

A DBS lead connector anchoring technique was implemented at our institution in March 2016. This consisted of suturing the connector bulb to the fascia inferior to the incision in the posterior parietal region using non-absorbable sutures. We retrospectively reviewed all surgeries for DBS from March 2013 to March 2017. All cases were performed by a single surgeon in a staged fashion with implantable pulse generators (IPG) being placed within a week from electrode placement. The incidence of lead fractures, lead connector migration, scalp erosion, and connector site infections were calculated for both groups.

Results

A total of 238 patients underwent placement of 199 electrodes and 185 IPGs during the study period. Of these, 148 and 37 IPGs/connecting cables were implanted before and after the start of the anchoring technique, respectively. Follow-up time ranged from 42-52months in the pre-anchoring group and 10-22months in the post-anchoring group. There were 4 lead connector migrations, 3 lead fractures (1 complete, 2 incomplete), and 2 infections in the pre-anchoring group. There were no symptomatic electrode fractures, lead connector migrations, scalp erosions, or connector site wound infections in the post-anchoring group.

Conclusions

Implanting the IPGs within a week from electrode placement avoids the need to manipulate scarred down lead cables which could cause fractures and lead migrations. It is possible to secure the bulb away from the incision thereby minimizing the risk of skin erosion while maintaining a low profile without the need for bone contouring.

572 Is MER Mandatory for DBS In Parkinson's Disease- A Clinical Study

Jitin Bajaj; Manmohan Singh

Introduction

Deep brain stimulation (DBS) is now proven to be an effective therapy for advanced Parkinson's disease (PD). Traditionally it is done under microelectrode (MER) guidance. Though it increases the accuracy but at the cost of multiple electrodes traversing the brain which increases chances of hemorrhage, duration of surgery, and cost. We retrospectively analyzed our data to compare clinical outcomes of patients who underwent DBS with and without MER.

Methods

The study was done at a single center specialized for DBS. Until 2013 all advanced PD patients underwent subthalamic (STN) DBS under MER guidance, and since 2014 without MER guidance. Preoperative and postoperative UPDRS were compared for both the groups. Primary outcome was an improvement in UPDRS to the on-stage Levodopa response. Secondary outcomes were hemorrhage rate, infection, and duration of surgery.

Results

Total 68 (20 females) patients with mean ± SD age of 56 ± 9.07 years underwent STN-DBS. 39 patients underwent MER recording (group A), and 29 not (group B). Mean UPDRS in the off stage of group A and B was 68.43 and 58.50, respectively, (P=0.137), and in on stage was 27.29 and 25.22, respectively (P=0.688). Postoperatively optimum UPDRS reached was 28.17 and 23.78 (P=0.207). Percentage improvement in tremor was 82.67 and 82.06 (P=0.926), rigidity was 78.24 and 74.29 (P=0.518), bradykinesia was 73.53 and 64.52 (P=0.082), and dyskinesia was 86.24 and 88.81 (P=0.71). Drugs could be reduced in all patients. There was one infection (requiring replacement) and one case requiring pallidotomy instead of STN-DBS due to no benefit intraoperatively, both in group A.

Conclusions

After attaining adequate experience with stereotaxy and DBS, one can forego MER in STN-DBS. It can save valuable operative time and decrease hemorrhage risk.

573 Combined Strain Relief Loop Failure and Lead Stiffness as a Cause of Lead Retraction In the St. Jude Infinity System: A Technical Note

Jessica Wilden

Introduction

Commercial DBS systems include a mechanism for securing the brain lead to the skull to prevent movement of the electrode tip. Nonetheless lead retraction has been noted, though the mechanism remains unclear. We describe failure of a DBS strain relief loop combined with decreased elasticity of the Infinity DBS lead as one possible cause of lead retraction.

Methods

A case report of simultaneous lead migration, and subsequent lead revision, is presented in a Parkinson's patient treated with bilateral STN DBS using the St. Jude Infinity System.

Results

71M underwent bilateral DBS STN lead placement using interventional MRI. Immediate postoperative scans demonstrated leads in excellent position. Two weeks later, patient underwent routine dissection of the distal leads with connection to lead extenders/generator. No excessive manipulation occurred. Postoperative head CT, for headache, demonstrated ~8 mm retraction of the lead tips. X-ray showed no change in the shape/radius of the strain relief loop for leads. DBS leads were revised. Severe scar had encased the extra-cranial brain leads. Lead retraction was confirmed by examining a black mark on each lead made at the original surgery immediately above the burrhole exit; at revision, these marks were several millimeters beyond the edge of the locking device rim despite intact locking devices.

Conclusions

Scar formation may occur around strain relief loops following DBS lead placement. Envelopment of leads by pericranium may prevent loops from tightening with distal pressure during surgical manipulation or patient movement, which may transmit any distal pressure directly to the locking device exit point. Commercial devices are not designed to withstand even mild tension with a break-point of ~0.6 lbs. The St. Jude Infinity lead is stiffer than the Medtronic lead to reduce its likelihood of in vivo damage; this reduced elasticity may make it more prone to movement from mild connector site manipulation.

574 Comparison of Intraoperative CT with Postoperative MRI Coordinates in the Placement of Deep Brain Stimulation Electrodes

Mena Said; Kiarash Shahlaie; Lin Zhang; Fady M. Girgis

Introduction

Deep brain stimulation (DBS) is an effective therapy for Parkinson's disease. Accurate lead placement in the subthalamic nucleus or globus pallidus is critical to ensure therapeutic effects and to minimize side effects. Intraoperative computed tomography (iCT) can be used to target and confirm lead position. The objective of our study is to compare the accuracy of lead placement using iCT relative to postoperative magnetic resonance imaging (MRI).

Methods

We conducted a retrospective study on 31 patients who underwent insertion of 57 DBS leads from August 2015 to December 2017 for Parkinson's disease, and who had iCT and postoperative MRI studies. Three patients had staged surgeries and the coordinates from each surgery were included in the analysis for the respective lead. Imaging studies were fused using Medtronic StealthStation"! S7. Lead position was calculated on iCT and postoperative MRI independently, and the absolute differences between the x, y, and z coordinates along with the Euclidean vectors were calculated.

Results

The mean absolute differences ± standard error of the mean for the x, y, and z coordinates were 0.013 ± 0.093 mm (p=0.89), 1.22 ± 0.14 mm (p<0.001), and 1.55 ± 0.15 mm (p<0.001), respectively. The average Euclidean vector was 2.44 ± 0.11 mm (p<0.001).

Conclusions

Based on this series, there exists a significant difference between iCT and post-operative MRI DBS lead coordinates. While the difference is small, further investigation is required to determine whether this difference is of clinical significance.

575 Biophysical Reconstruction of the Signal Conduction Underlying Cortical Evoked Potentials Generated by Subthalamic Deep Brain Stimulation

Kabilar Gunalan; Cameron C. McIntyre

Introduction

Direct stimulation of the hyperdirect pathway has been linked to therapeutic benefit in subthalamic deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD). Cortical evoked potentials generated by subthalamic DBS represent an electrophysiological signal that can be associated with hyperdirect pathway activation and represent possible biomarkers for use in closed-loop DBS control systems. The objective of this study was to quantify the axonal conduction biophysics of corticofugal axons directly stimulated by subthalamic DBS and reconcile those findings with cortical evoked potential results that suggest a very fast component (R1) occurring ~1 ms after the stimulus pulse, as well as a slower component (R2) that reaches its peak in ~6 ms.

Methods

We used a detailed computational model of human subthalamic DBS to quantify axonal activation and conduction. Signal propagation to cortex was quantified for medium (5.7 µm), large (10.0 µm), and exceptionally large (15.0 µm) diameter corticofugal axons.

Results

Subthalamic stimulation of hyperdirect axons with 5.7 µm corticofugal axon diameters propagated action potentials to cortex with timings that matched very well with the R2 evoked potential, representing a convergence between histological, biophysical, and electrophysiological results. However, only the 15.0 µm axon models, which would be extremely rare, generated signals that could approach the R1 timing.

Conclusions

Origin of the R1 signal remains unclear, but R2 can be attributed to antidromic activation of the hyperdirect pathway.

576 Redundant Population Encoding of Movement by the Basal Ganglia and Thalamus

Ifije Ohiorhenuan; Enrique B.S. Arguelles; Arash Maskooki; Daniel R. Kramer; Aaron Robison; Mark A. Liker; Terence Sanger

Introduction

The use of deep brain stimulation (DBS) to treat children with secondary dystonia is challenging since the optimal target can be difficult to localize. At Children's Hospital of Los Angeles, patients with secondary dystonia, undergo a monitoring procedure, using depth electrodes to identify DBS targets. Single-cell action potentials, LFP, EEG and EMG activity are recorded over a period of 5 days. This provides a wealth of neurophysiology data over a range of spatial scales in awake patients. Here, we focus on characterizing multineuron interactions in basal ganglia and thalamic nuclei.

Methods

We record from basal ganglia and thalamic nuclei in children with secondary dystonia. Spike data is sorted and the firing patterns of groups of 3-5 neurons are measured. We fit three types of maximum entropy models: an independent model, without interactions between neurons; a pairwise model with interactions between all pairs of neurons; and a common-input model where all neurons receive a common synaptic drive. We then compare the rates of firing patterns observed to the model predictions. To determine the effect of movement, we perform the described analysis conditioned on left or right-sided EMG activity.

Results

We find that the independent model frequently fails to predict the observed firing patterns, but the pairwise model is an almost perfect model. Interestingly, the common-input model, which has fewer parameters than the pairwise model, performs almost as well. Using the firing patterns conditioned on movement direction, we find that correlations between neurons act to decrease the amount of information transmitted a form of redundant coding.

Conclusions

Pairwise interactions nearly completely account for the structure of multineuron firing patterns within the basal ganglia and thalamus. A model of common synaptic input is a reasonable approximation. Movement encoding is redundant allowing for information transmission even when some data is lost.

577 Intraparenchymal Cystic Formation Around the Deep Brain Stimulator Lead: Three Case Reports

Yasaman Kianirad; Mark J. Nolt; Kenny Tan; Cindy Zadikoff; Michael Rezak; Joshua M. Rosenow

Introduction

Deep brain stimulation (DBS) is a well-established treatment for the management of medically refractory movement disorders. Various adverse events have been described. Formation of a cyst along the DBS lead is a less well-recognized, infrequent, and under-reported complications following surgery.

Methods

We present three cases of cyst formation following DBS lead implantation.

Results

Case 1: A 68-year-old female with idiopathic PD underwent bilateral STN DBS surgery. Ten weeks after right STN surgery, she began falling, developed dysarthria and dysphagia, and had left hemi-body weakness. MRI revealed fluid collection around right DBS lead. MRI repeated after two weeks showed unchanged cystic lesion. MRI four weeks later showed increase in cyst size. Due to gait and speech decline, lead was removed. MRI four months later showed decreasing size of cyst, and patient speech and gait improved. Case 2: A 72- year-old male with essential tremor underwent left VIM DBS surgery. MRI one day and two weeks after surgery showed peri-electrode edema with no clinical correlates. MRI 3.5 months after surgery revealed cystic formation which remained unchanged after one month. No neurologic deficit was observed. MRI at one year showed decreasing size of cyst. Case 3: A 68-year-old female with essential tremor underwent bilateral VIM DBS surgery. Initial post-operative MRIs revealed no edema or cyst. She developed dysarthria and balance problems 3.5 months after left DBS surgery and MRI showed edema around left electrode. Two week follow-up MRI revealed cystic formation around left electrode. Given persistent neurologic deficit, left lead was removed. MRI one month later demonstrated resolution of the cyst.

Conclusions

We report three cases of cystic formation around the DBS lead. To date, six reports describe this complication in ten patients. Conservative management may be successful, but in most cases, leads must be removed to decrease cyst size or reduce neurologic deficit.

578 Implementation of Quantitative Error-checking Algorithm for the FrameLink Fusion Paradigm with Calculation of Absolute Fusion Error Rate

John Frederick Burke; Dominic Tanzillo; Philip A. Starr; Paul S. Larson

Introduction

Traditional deep brain stimulation (DBS) surgery relies heavily on co-registration or fusion of computed tomography (CT) and magnetic resonance (MR) brain imaging. Image fusion is not an exact science, and the most common DBS planning software (Medtronic StealthStation® FrameLink) does not provide quantitative error measurements of image fusion. This requires the surgeon to make qualitative judgements regarding co-registration accuracy and make corrections if desired. Analysis of accuracy has historically been difficult as the software does not allow screen shots during the fusion process.

Methods

22 DBS patients were included. Patients had both CT and MRI scans taken in the immediate pre-operative period. We took 8 photographs of the StealthStation® screen during fusion using a DSLR camera on a tripod at a fixed distance. Photos were taken of CT, MRI, and merged CT-MRI scans at two different axial locations. Standardized points and control points were identified for both CT and MRI scans, and the distances between these points were compared in the un-edited fused images. The thickness of the skull was also compared.

Results

The average error in fusion was 1.4 mm (S.D. 3.2 mm). Comparison of skull thickness between the CT and MR images at identical locations showed a significant difference between the two ($p=3.9e-5$, $T=5.18$, D.F.=21).

Conclusions

There are non-trivial errors in the image fusion process used in modern DBS software. As the field reports accuracy in clinical studies and moves toward purely image-guided "asleep DBS", these errors must be recognized and accounted for. Clinicians should demand quantitative metrics on co-registration when merging CT and MR images.

579 Outcomes Following Deep Brain Stimulation Lead Revision or Reimplantation for Parkinson's Disease

Leonardo A. Frizon; Sean J. Nagel; Francis May,; Jianning Shao; Andres Maldonado-Naranjo; Hubert H. Fernandez; Andre Machado

Introduction

Deep brain stimulation (DBS) is an established treatment for the management of Parkinson's disease (PD), tremor and dystonia. Patient selection, target choice and surgical accuracy are the foundation for a successful DBS outcome. However, in some cases, revision or reimplantation is needed due to limited benefits, device failure or infection involving the hardware. There are relatively few published series describing the outcomes after lead revision or reimplantation. In this study, we present our outcomes after revision or reimplantation surgery in patients with infections, device failure or unsatisfactory results after DBS surgery for PD.

Methods

Demographic data, indication for removal or revision, procedure time, outcomes and lead location for reimplants were analyzed for all patients who underwent DBS for PD between 2010 and 2016 at our institution. The Movement Disorders Society-Unified Parkinson Disease Rating Scale Motor subscale (MDS-UPDRS III) scores were compared prior to and 6 months after re-implantation. Lead location were analyzed before removal and after re-implant or revision.

Results

Our final sample included 25 patients who underwent 34 lead removals. Thirteen patients had eighteen leads reimplanted after removal. There was significant improvement in the motor scores after revision surgery among the patients who had the lead revised for a suboptimal outcome ($p=.025$). The mean vector distance of the new lead location compared to the previous location was 2.16mm (SD=1.17), measured on an axial plane 3.5 mm below the AC-PC line. When these leads were analyzed by subgroup, the mean distance was 1.67 mm (SD=0.83) among patients treated for infection and 2.73 mm (SD=1.31) for those with suboptimal outcomes.

Conclusions

Patients with Parkinson's disease who underwent reimplantation surgery due to suboptimal outcome may experience significant benefits. Reimplantation after surgical infection seems feasible and overall safe.

580 Multiple Single Unit Activity in Ventral Intermediate Thalamus of Essential Tremor Patients During Intention Tremor

Pankaj Sah

Introduction

Essential Tremor is the most common movement disorder; however its pathophysiology is still unclear. Severe cases have been treated successfully with deep brain stimulation of the Ventral Intermediate nucleus of the Thalamus (Vim).

Methods

Microelctrode recordings were made from 9 patients as part of the intra-surgical exploration during the implantation of deep brain stimulation electrodes. Stereotactic surgery was performed with a Cosman-Roberts-Wells CRW stereotactic head frame. Image based targeting of the Vim was performed on MRI and stereotactic-CT fused images on a Medtronic Stealthstation machine. Recordings were taken with a single microelectrode, with a Medtronic Leadpoint system, on a linear trajectory at one millimeter steps. Only recordings taken up to 5 mm above the lower border of the Vim were considered for the analysis. Signals were acquired with Spike2 software. Unit spike sorting was based on a supevised hierachical clustering with Wavelet and principal components decomposition and performed with custom Matlab code. Accelerometric signal of the contralateral hand was also acquired, during intention tremor and rest state. All patients were awake during recording.

Results

Spike sorting yielded 66 units (27 single cell activity and 39 multi cell activity) recorded during rest (n= 54) and tremor (n= 32). We did not find differences in firing rate, action potential duration, burst index, mean spikes per burst, burst rate and proportion of spikes in bursts between rest and tremor (Wilcoxon rank-sum test $p>0.05$). Four out of 23 units tested during tremor were phase locked at tremor frequency (4-5Hz). Two out of 28 units were phase locked at 15-20 Hz during baseline (Rayleigh test, corrected $p<0.01$). Local Field Potential (LFP) was coherent with tremor at tremor frequency (4-5 Hz), with a tendency of tremor to lead the LFP by a variable delay time (~250-650 ms). Tremor frequency appeared to fluctuate at ~0.5Hz, within tremor epoch.

Conclusions

We found a periodical fluctuation of the tremor frequency at ~0.5 Hz both in LFP as well as the accelerometer signal (FIG5), which to our knowledge is a new pathological feature of intention tremor.

581 Impact of Deep Brain Stimulation on Cognitive Outcomes in Patients with Parkinson's Disease

Mark K. Lyons; Allison Hansen; Janina Krell-Roech; Kristin A. Kirlin; Martin M. Limback-Stokin; Kimberly Roesler; Stefanie N. Velgos; Yonas Geda; Shyamal H. Mehta

Introduction

The impact of deep brain stimulation (DBS) surgery on cognition in patients with Parkinson's Disease (PD) can be a major obstacle to quality of life in this population. We investigated the effects of DBS of the globus pallidus pars interna (GPi) or subthalamic nucleus (STN) on cognitive function six months following DBS surgery in patients with medically refractory PD.

Methods

A historical cohort study of 32 patients with medically refractory PD undergoing bilateral GPi DBS (13) or STN DBS (19)were studied. All patients underwent neuropsychological batteries at baseline and six months post DBS surgery. Boston Naming Test (BNT), Wechsler Adult Intelligence Scale-IV Verbal Comprehension Index (WAIS-IV VCI),Wechsler Adult Intelligence Scale-IV Working Memory Test (WAIS-IV VMI) and Wechsler Adult Intelligence Scale-IV Processing Speed Test (WAIS-IV PSI) were used.

Results

We observed no significant difference in GPi patients between baseline and follow-up test scores on any of the four neuropsychological tests. STN patients showed significant cognitive decline on follow-up as compared to baseline on three of the four cognitive tests: WAIS-VCI (104.95 [SD 12.9] vs. 100.89 [12.4]; $p=0.0044$), WAIS-WMI (99.32 [14.1] vs. 92.68 [12.5]; $p<0.001$), and WAIS-PSI (92.95 [12.9] vs. 81.89 [12.2]; $p<0.001$). When we compared the changes in baseline and follow-up scores between the GPi and STN patients, we observed a significant difference on three (WAIS-VCI, WAIS-WMI, WAIS-PSI) of the cognitive tests

Conclusions

Our results indicate that STN DBS, but not GPi DBS, is associated with a less favorable cognitive outcome in the domains of processing speed, attention/concentration, and language. From a cognitive health perspective, these findings suggest that GPi may be a preferred target for DBS in patients with medically refractory PD.

582 Studying the Effect of Subthalamic Stimulation and Dopamine-dependent Therapy on Human Behavior Analysis using LFP Signals

Adam O. Hebb; Hosein Golshan Mojdehi; Joshua Nedrud; Mohammad H. Mahoor

Introduction
Current clinically available deep brain stimulation (DBS) therapies for Parkinson's disease (PD) are all open-loop and are unable to adapt to the ever-changing patient, medication, and disease states. A closed-loop DBS system that utilizes appropriate physiological control based on patients' predicted behavior may improve therapeutic results. In this study, we develop a behavior classification method robust to stimulation to label patient actions even in the presence of therapy. Furthermore, we investigate the effect of medication and stimulation on the increased beta power associated with PD.

Methods
Three participants were implanted with DBS leads in the subthalamic nucleus (STN). During two data collection sessions from the implanted leads, one "on" medication and one "off" medication, the participants were cued to perform a series of 60 "button press" then "reach" actions with and without therapeutic stimulation. We transformed the bipolar re-referenced local field potentials (LFP) into their time-frequency representation and used the beta frequency range (13-30Hz) as input to a support vector machine (SVM) classifier. Additionally, we used Welch's power spectral density (PSD) estimate to evaluate the effect of the medication and stimulation on the beta power of LFPs.

Results
We obtained a classification accuracy of 87%, 85%, and 87% for stimulation "off", "on", and "combined" data sets using a SVM classifier. An analysis of variance (ANOVA) for the PSDs of the four combinations of stimulation "on/off" and medication "on/off" show beta power is suppressed significantly when the patients take medication (p-value<0.002) or receive therapeutic stimulation (p-value<0.0003).

Conclusions
The results show that STN-LFPs contain useful information for human behavior recognition. The high-frequency stimulation pulse (~140 Hz) had limited impact on the classification performance. This is a precursor for designing the next generation of closed-loop DBS systems.

583 Spreading Depolarizations and Transient Aphasia in Chronic Subdural Hematoma Patients

Bornali Kundu; Ryan Carlson; Lee Chung; KC Brennan; John David Rolston

Introduction

Spreading depolarizations (SDs) are electrical waves in cortical gray matter that result from a mismatch in energy demand and availability in cells[1]. SDs have been recorded in multiple neurosurgical conditions and may be a mechanism of secondary brain injury following an initial insult[1-2]. Here we present two cases that suggest SDs may be related to ongoing neurological deficits such as aphasia in patients with subdural hematoma (SDH), where SDs have been demonstrated but incompletely explored.

Methods

Two patients presented with acute onset aphasia and imaging consistent with acute-on-chronic subdural hematoma. They underwent hemicraniotomies for SDH evacuation and intracranial electrode placement in the symptomatic hemisphere. SDs were monitored in the intensive care unit (ICU) postoperatively. Electrocorticography (ECoG) data were acquired using strip and depth electrodes, placed on the cortical surface, using the COSBID study group protocol[3]. The presence of aphasia were recorded hourly by trained ICU staff. Data were analyzed offline using MATLAB. The temporal relationship between SDs and the presence of aphasia is reported.

Results

41 hours and 21 hours of data were collected respectively for patient 1 and patient 2. 10 and 6 SDs occurred during that time, respectively. For both patients, as SDs cleared in time, aphasia improved. For patient 1, aphasia returned with recurrence of SDs, 27 hours after initial implantation. Concurrent data were collected between depth and strip electrodes. Data from these two modalities show agreement for the SD-time-locked events. 3 months out, patient 1's aphasia resolved. Patient 2 continued to have word finding difficulty requiring readmission, but at 2-month follow up, her symptoms improved.

Conclusions

These data suggest there may be a temporal relationship between neurological deficits and the presence of SDs. This protocol will continue to recruit patients with chronic SDH. The results may help validate SDs as clinically significant events in SDH patients requiring monitoring.

584 The Comprehensive Anatomy of the Foramen Ovale as it Relates to Percutaneous Stereotactic Radiofrequency Rhizotomy: A Cadaveric Study of Dry Skulls

Smruti K. Patel; Adel El-Nashar; Almaz Kurbanov; Kisenya Zervera; Ryan Hatch; Enoch Kan; Jeffrey T. Keller; Andrew W. Grande

Introduction

Trigeminal neuralgia is a serious condition resulting in lancinating, episodic facial pain. Percutaneous stereotactic radiofrequency rhizotomy is frequently used to treat trigeminal neuralgia. A thorough understanding of the microsurgical anatomy of the foramen ovale and surrounding structures is required for efficient, effective and safe use of this technique. This study was undertaken to define the anatomical variations of the foramen ovale (FO) and to assess cannulation difficulty, as well as the potential risk of injury to surrounding structures.

Methods

Bilateral foramina from 174 adult human dry skulls (348 foramina) were analyzed in both an anatomic and surgical orientation using photographs obtained from standardized projections. Measurements were obtained of multiple variables including shape, size, presence of adjacent structures, and the morphometric variability effect on cannulation.

Results

From the anatomic exocranial view, 6 distinct anatomical shapes of the foramen ovale were identified as well as 5 anomalous variants. From the surgical view, 6 distinct procedural shapes were identified. When the surface area (SA) of the FO was measured in the surgical view, there was a significant loss of SA compared to the anatomic exocranial view. On average, the SA lost was 18.5 5.7%. Morphometrically, we found significant variability in foramen size, and obstruction of the foramen in up to 7.8% from a calcified pterygoalar ligament. Importantly, we found that 8% of foramina were very difficult to cannulate and the risk of inadvertent cannulation of the foramen lacerum was 12%.

Conclusions

We determined that there is significant variability in the shape and size of the FO, which we believe impacts the ability to safely and effectively cannulate this structure. Preoperative imaging with a 3D head CT may be of value in predicting difficulty of cannulation and guide treatment decisions when considering the use of a percutaneous approach over microvascular decompression or radiosurgery.

585 Can DBS Modulate Network Activity to Relieve Pain in Parkinson's Disease?

Marisa D. DiMarzio; Ileana Hancu; Eric Fiveland; Julia Prusik.; Michael Gillogly; Radhika Madhavan; Suresh Joel; Jennifer Durphy; Eric Molho; Era Hanspal; Damian Shin; Julie G. Pilitsis

Introduction

While deep brain stimulation (DBS) is a well-validated treatment of motor symptoms in Parkinson's disease (PD), its efficacy to treat non-motor symptoms, such as chronic pain, remains unclear. Chronic pain affects up to 83% of PD patients. Functional MRI can provide insight into the pathophysiology of chronic pain in PD and how DBS modulates it. To date, fMRI has focused on thermal stimuli response, which is less clinically relevant and no work has looked at DBS ON imaging in presence of a noxious mechanical stimuli.

Methods

PD patients with chronic pain underwent task-based fMRI. Data was compared to PD patients who had STN DBS implantation/programming. All cohorts were exposed to a noxious mechanical stimulus. Baseline pain scores via Kings Parkinson Disease pain scale (KPDPS) and motor score with the Unified Parkinson's Disease Rating Scale motor component (UPDRS-III) were documented. Model-based voxel-wise General Linear model (GLM) using pain-off data was used to determine regions affected during pain-on periods. For group analysis, previous images of the individual subjects were used to determine voxel-wise statistics.

Results

Both cohorts found the noxious mechanical stimuli equally as uncomfortable (5.3 ± 1.04 vs. 6.0 ± 0.54 on numeric rating scale (NRS)). Individual analysis of fMRI data from control PD patients and PD patients with DBS OFF revealed similar activity in the primary somatosensory cortex (S1) and primary motor cortex (M1) in 78% and 67% of subjects respectively ($p<0.05$). Further group analysis of these cohorts confirmed sensory thalamus, S1 and M1 activation. In the cohort with DBS implanted and turned ON, individual and group analysis revealed a decrease in S1 and M1 activation.

Conclusions

PD patients without DBS and DBS OFF have similar activation in S1 and M1. Group analysis reveals that DBS reduces activation in these areas. We speculate that DBS inhibits the lateral pain pathway causing a reduction in pain perceived.

586 The Incidence of Vascular Conflict with the Trigeminal Nerve in Cluster Headache

Tsinsue Chen; Arthur Andre; Indran Davagnanam; Daisuke Danno; Ludvic Zrinzo; Manjit Matharu

Introduction

Cluster headache (CH) is one of the most disabling primary headache syndromes. Although neurovascular conflict is implicated in facial pain syndromes such as trigeminal neuralgia, its role in CH has not been systematically reviewed. In this study, we assess the incidence of radiographic arterial and venous conflict with the trigeminal nerve in symptomatic versus asymptomatic trigeminal nerves in a cohort of patients with CH.

Methods

Patients with confirmed CH at a single institution underwent high-resolution MRI of the prepontine cistern between 2007 and 2017. Prospectively acquired images were retrospectively reviewed by a neuroradiologist and two neurosurgeons blinded to symptom severity and lateralisation. Each trigeminal nerve was classified into one of the following groups based on its relationship to adjacent vasculature: (1) no vessel within 1 mm, (2) vessel within 1 mm, (3) vascular contact, (4) vascular distortion of the nerve and (5) vascular contact nerve atrophy or signal change.

Results

136 patients (mean age at imaging: 44.5 years, mean age of symptom onset: 31.0 years) had 153 symptomatic and 119 asymptomatic nerves (55 left-sided; 64 right-sided; 17 side-alternating attacks). The incidence of arterial conflict (groups 3, 4 and 5) was significantly higher in symptomatic compared to asymptomatic nerves (40.5% vs. 26.9%, $p=0.02$). The incidence of venous conflict was not significantly different between symptomatic versus asymptomatic nerves (42.5% vs. 42.0%, $p=0.94$).

Conclusions

We hypothesize that arterial contact is neither required nor sufficient to drive CH attacks but that it may interact with a central (hypothalamic) generator to drive symptoms in a subgroup of patients. These findings suggest a rationale for microvascular decompression of the trigeminal nerve in patients with refractory CH and radiological arterial contact with the nerve on the symptomatic side.

587 Extended DREZ-lesion for Relieving Intractable Arm Pain Following Brachial Prexus Avulsion Injury. What Occurs at the Injured Dorsal Horn

Makoto Taniguchi; Keisuke Takai; Hirokazu Iwamuro

Introduction

The arm pain following brachial plexus avulsion injury (BPA) is one of a typical neuropathic pain of the spinal cord origin. The pain contains at least two different components, namely continuous one and shooting one, of wich the latter is more burden to the patients. From unknown reason, the pain intensity increase with time and become more bothering. Although lacks evidence, DREZ-lesion is known to be a practically only one effective treatment of choice. In this presentation, our modified DREZ-lesion technique and its results will be presented.

Methods

So far 17 serial cases of BPA were operated in a single hand. Detailed patients background and surgical maneuvers were described previously. In short, care was taken to include Rexed's layer V in the area of surgical destruction. In the last 4 cases, instead of destruction and absorb, the gliotic tissue are obtained for microscopical inspection, where H&E, KB, Neu N, NF, and CD68 staining were carried out.

Results

1) Almost complete and long-lasting pain relief with the longest follow up of 9 years were realized without any additional motor deficit. 2) The most prominent gliotic change were seen at the segment compatible with the most painful area of each patient. 3) Microscopical inspection of the specimen showed, although a few, neurons in the obtained specimen form the dorsal horn. And, prominent ballooning of microglia cells were observed in some specimen.

Conclusions

Our extended DREZ-leison int Rexed;s layer V supplied more complete and longstanding pain relief to the arm pain following BPA. Prominent activation of microglia at the injured dorsal horn suggests a new neural network formation as a mechanism of pain intensity exaggeration with years and shooting character of the pain.

588 Placement and Anchoring of Craniofacial Neurostimulation Electrodes: Technical Note

Robert Wagner Bina; Willard Stein Kasoff

Introduction

Peripheral neurostimulation (PNS) for medically-refractory craniofacial pain and headache is an emerging alternative to traditional surgical approaches. Technical problems with craniofacial PNS have included electrode migration and erosion, limiting the utility and cost-effectiveness of this procedure. We present an improved method for craniofacial PNS surgery which introduces a separate incision for electrode anchoring at the parietal boss. This technique simplifies the procedure and greatly reduces rates of erosion and migration.

Methods

Consecutive cases of permanent craniofacial PNS placement by a single surgeon over 36 months were reviewed for surgical technique and technical outcomes. Electrodes were placed via anterior temporal stab incisions with open anchoring to the pericranium at a separate parietal incision.

Results

16 systems (53 electrodes) were implanted in 14 patients. Median follow-up was 11 months (range, 5 29 months). Electrode placement was successful in all cases with no intraoperative complications. There was 1 lead migration (6.3% per patient; 1.8% per lead) and no cases of erosion. 2 patients (14.3%) required explant for infection, 1 of whom was successfully reimplanted. 3 patients (21.4%) underwent surgical revision other than for infection.

Conclusions

Presented is an improved surgical technique for craniofacial PNS placement and anchoring which (1) minimizes lead migration, (2) improves patient comfort, (3) reduces the risk of skin erosion, and (4) optimizes post-surgical lead identification.

589 Complications of Spinal Cord Stimulation: Initial Five-year Experience

Vijay M. Jafarov; Alexander Dmitriev; Natalia Denisova; Eugenia Amelina

Introduction

Spinal cord stimulation (SCS) has been established as safe and efficient method for the treatment of different pain conditions. The reported incidence and severity of complications is variable. Here, we report own the SCS-related complications over the initial 5 years, compare our results with those reported in the literature, and attempt to identify keys and predictors to avoidance.

Methods

Retrospectively we performed analysis of complications that required revision in 207 patients who primary underwent SCS in our department between 2013 and 2017. Percutaneous leads were used in this series. Statistical analysis was conducted using Welch's t-test, Kaplan-Meier curves and Cox proportional-hazards regression.

Results

Among 207 patients, surgical revision occurred in 42 patients (20.2%). In addition, 9 (4.3%) patients of 42 required more than one revision. The most frequent reasons were migration of system's component (12%), hardware dysfunction (4.3%), pocket pain (3.3%) and loss of therapeutic effect (2.8%). Neurological deficit was in one rare case with spinal cord compression due to severe epidural fibrosis. Removal of the SCS was performed in 13 cases. Younger age was identified as predictors of lead migration ($p<.001$). No association was found between other measures (gender, BMI, site of implantation, electrode level of implantation, direction of lead migration, pain condition, device manufacturer) and complications.

Conclusions

SCS appears as a safe method. Although, the results of this analysis comparable with the previous reports the complication rate remains high.

590 Prospective Randomized Study Comparing Manual vs. Automatic Position-Adaptive Spinal Cord Stimulation with Surgical Leads

Kara D. Beasley; Christie Zakar; Vinod Kantha; Sigita Burneikiene

Introduction

The primary purpose of this study was to establish the extent that chronic pain patients implanted with laminectomy-type leads experience position-related variations in spinal cord stimulation therapy. The secondary objective was to investigate the effects of manual versus automatic position-adaptive spinal cord stimulation on clinical outcome.

Methods

A total of 18 patients were enrolled in a single-center prospective randomized clinical study with a two-arm crossover design: manual or automatic position-adaptive stimulation. All patients were followed for a total of 5 months with clinical outcomes and stimulation parameters collected.

Results

Clinical outcomes improved significantly at all time points for ODI ($p=.0039$), VAS leg ($p=.0082$), Pittsburg Sleep Quality Index ($p=.034$), and at 2 months for VAS back pain scores compared with baseline scores. There were no statistically significant changes in pain medication scores ($p=.73$). In addition, we did not detect any statistically significant differences for medication use (6.8 vs. 6.6; $p=.77$), ODI (33.4 vs. 31.5; $p=.28$), VAS for back (4.3 vs. 3.5; $p=.16$) or leg pain (3.3 vs. 3.3; $p=1.0$), and PSQI (8.9 vs. 8.6; $p=.65$) scores in manual vs. automatic patient groups. The patients reported higher Likert scale satisfaction rates with automatic stimulation (mean 1.7; 95% CI = 1.1   2.3). There were no statistically significant amplitude or impedance differences found between manual and automatic stimulation in any of the body positions. The highest reduction in therapeutic stimulation amplitudes was recorded in the supine position: 74% of the upright body position for manual (95% CI = 64%   83%) and automatic (95% CI = 65%   83%) stimulation.

Conclusions

Similar variations were reported for manual or automatic stimulation intensity in response to positional changes, but the patients were much more satisfied when using position-adaptive stimulation for relief of their back and leg pain.

591 Deep Brain Stimulation of the Medial Forebrain Bundle for Treatment Resistant Depression

Albert J. Fenoy; Paul Schulz; Sudhakar Selvaraj; Christina Burrows; Giovana Zunta-Soares; Joao Quevedo; Jair C. Soares

Introduction

Deep brain stimulation (DBS) to the superolateral branch of the medial forebrain bundle (MFB) has been reported to be effective in rapidly improving treatment resistant depression (TRD). This report is an update to our recently published results (Fenoy et al., 2016).

Methods

In this analysis of an ongoing study, we assessed the efficacy of MFB-DBS in a cohort of eight TRD patients over a 52-week period using improvement on the Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary outcome measure. Implanted patients entered a 4-week single-blinded sham stimulation period prior to stimulation initiation.

Results

Upon stimulation at target intraoperatively, responders reported immediate increases in energy and motivation. There was a significant mean change in mood during the 4 week sham stimulation phase (34% mean MADRS reduction, $p = 0.03$), but no significant difference upon stimulation initiation at 1 week relative to end sham. However, the difference in MADRS score between baseline and 2 weeks of active stimulation was significant (mean change = 17 pts, 49% reduction, $p < 0.001$). One patient withdrew from study participation. At 26 weeks, 5 of 6 remaining patients have >50% improvement of MADRS (mean improvement = 27 pts, 77% reduction, $p = 0.002$). At 52 weeks, 4 of remaining 5 patients continue to have >70% decrease in MADRS scores relative to baseline. 2 patients are currently active in the study and have not completed all assessments. One patient failed to respond. Evaluation of modulated fiber tracts reveals significant common frontal connectivity to the target region in all responders.

Conclusions

This study of MFB-DBS confirms rapid anti-depressant effects are observed with stimulation, as reported by Schlaepfer et al. (2013). Although the insertional response itself is significant, the effect becomes more pronounced with time after stimulation onset.

592 Tractography Analysis of Capsulotomy for Treatment Resistant Major Depression

Josue Moises Avecillas-Chasin; Trevor Hurwitz; Christopher Honey

Introduction

Bilateral anterior capsulotomy (BAC) is an effective surgical procedure for patients with major depression (MD). The anterior limb of the internal capsule (ALIC) carries circuits associated with emotion, and cognition. Here, we analyzed the connectivity of the BAC lesions to identify 'fingerprints' associated with clinical outcomes.

Methods

We retrospectively analyzed ten patients following BAC. These patients were divided into good or poor outcome based on the Beck depression inventory (BDI) score at one-year follow-up. These patients were matched with 10 subjects obtained from a neuroimaging sample. The lesions were segmented and transferred to the native space of the matched subjects to generate group-averaged probabilistic 'fingerprints' associated with a given outcome. We also generated the major fibers of the ALIC (mesocortical, mesolimbic, and anterior thalamic radiations[ATR]) and analyzed if the lesion overlap with each of these fibers correlated with outcome.

Results

Six patients had good outcome (>50% improvement), four patients had poor outcome (25-50% improvement). The good-outcome map showed significant connections with limbic areas including ventromedial prefrontal, anterior cingulate, lateral orbitofrontal, and medial prefrontal cortex. The poor-outcome map showed significant connections with the same limbic areas and also significant stronger connectivity to associative areas including the dorsolateral prefrontal, ventrolateral prefrontal, and lateral orbitofrontal cortex. Nonparametric tests showed that in the good-outcome group, the involvement of the associative circuit was significantly less than the limbic circuit ($p=.002$). Conversely, in the poor-outcome group, there was no significant difference between the involvement of these circuits ($p=.099$). Finally, there was no significant difference in the involvement of the mesocorticolimbic tracts compared to the ATR in the two outcome groups ($p=.134$, $p=.347$).

Conclusions

Good outcome following BAC surgery is associated with interruption of key limbic areas and preservation of associative regions. Tractography would be helpful in identifying those fibers within the ALIC that need to be destroyed or preserved.

593 Stereotactic Radiosurgical Capsulotomy for Obsessive-Compulsive Disorder: Initial Results Using a "Goldilocks" 5-Shot Radiosurgical Plan

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Introduction

Obsessive-compulsive disorder (OCD) has a lifetime prevalence of 2 to 3%, and many patients are refractory to conventional pharmacological and behavioral treatments. Neurosurgical options including stereotactic radiosurgical capsulotomy (SRSC) have been used for decades in refractory patients, with symptomatic response rates of 40-65%. The most significant adverse event from these procedures is radionecrotic cyst formation and frontal lobe edema causing a dysexecutive syndrome, which is radiation dose dependent. We employed a radiosurgical plan with a novel 5-shot dose distribution, designed to be large enough to recapitulate the efficacy of earlier 2-shot procedures but conformal enough to reduce the chance of cyst/edema formation.

Methods

The radiosurgical plan consists of 5 4-mm shots per hemisphere, with 150 Gy maximum dose. The vertically stacked shot configuration uses sector blocking and weighting to produce a distribution elongated in the superior-inferior direction (Fig 1). The ventral-most shot is placed in the ventral portion of the anterior limb of the internal capsule bordering the ventral striatum in the coronal plane, and near the posterior putaminal border in the axial plane. Response was defined as >35% reduction in Yale-Brown Obsessive Compulsive Scale (YBOCS) score.

Results

Six patients with severe, refractory OCD have undergone the 5-shot SRSC (Figure 1). Of the 4 patients who are >6 months out, all 4 are responders, with mean YBOCS reduction of 50% (range 36-68%) at mean follow-up interval of 9 months (range 7-13). Dose-volume histograms demonstrated conformality, and low volumes at mid-range doses (~0.6 cc at 60 Gy). Thus far, follow-up MRIs have demonstrated minimal edema and no cyst formation (Fig 2). Other than brief (~1 month) mild fatigue, no other adverse events have occurred.

Conclusions

SRSC strives to deliver the "just right" dose of radiation: enough to create an effective lesion, but not enough to cause adverse events. Our initial results show response rates at least as high as those produced using previous treatment plans with higher radiation dose. Longer follow-up interval in more patients will determine whether the adverse event profile is improved with this plan. SRSC remains an attractive neurosurgical option for refractory OCD.

594 Deep Brain Stimulation Results in Greater Symptomatic Improvement in Tourette Syndrome than Medication or Behavioral Therapy: a Meta-Analysis

David Arnold Purger; Uma Mahajan; Alessandra Mantovani; Nolan Williams; Flint Martin Espil; Sherman C. Stein; Casey H. Halpern

Introduction

Deep brain stimulation (DBS) has emerged as a safe and effective therapy for severe, treatment-refractory Tourette syndrome (TS), a potentially debilitating disorder affecting approximately 1:2000 adults in the US. Recent studies have demonstrated that DBS is effective in reducing TS symptoms as measured by the Yale Global Tic Severity Scale (YGTSS), but no studies, to our knowledge, have compared the effectiveness of DBS with conservative therapy.

Methods

We performed a meta-analysis of studies investigating patient outcomes reported as YGTSS scores after DBS surgery, pharmacotherapy, and behavioral therapy. Single case reports and studies with participant mean age <16 years or without YGTSS data were excluded. Data were pooled using a random effects model of inverse-variance weighted meta-analysis (n=174 for DBS, 133 for medications, 201 for behavioral therapy). All DBS targets, all medications, and all psychotherapeutic modalities were pooled.

Results

DBS resulted in a significantly larger reduction in YGTSS total score (49.9% ± 17.5%) than pharmacotherapy (22.5% ± 15.2%, P=0.001) or behavioral therapy (20.0% ± 11.3%, P<0.001). The complication/adverse effect rate was 0.15/case for DBS (including 0.04 major complications such as infection and lead migration per case) versus 1.13/case for medications and 0.60/case for psychotherapy. Groups were demographically similar, though baseline YGTSS total score for DBS patients was 80.0 ± 9.8 (mean ± SD; total 100), significantly greater than the baseline score for patients in medication (54.1 ± 9.8) or behavioral (48.2 ± 2.3) trials (P<0.001). Notably, there was no difference in effectiveness of DBS between targets (P=0.792).

Conclusions

Our data suggest that, despite greater baseline symptom severity, TS patients undergoing DBS experience greater symptomatic improvement with surprisingly low morbidity as compared with pharmacotherapy and behavioral therapy. Randomized controlled trials are warranted to pursue regulatory approval of DBS as a mainstream therapeutic option for patients with severe TS.

595 Bilateral Globus Pallidus Interior Deep Brain Stimulation Combined with Capsulotomy for Tourette's Syndrome with Psychiatric Comorbidity

Chencheng Zhang; Haiyan Jin; Dianyou Li; Bomin Sun

Introduction

A current challenge lies in finding an effective and safe treatment for patients with severely disabling Tourette's syndrome (TS) and comorbid psychiatric disorders who fail to respond to conventional treatments. Here, we evaluate the utility of globus pallidus internus deep brain stimulation (GPi-DBS) combined with bilateral anterior capsulotomy in treating these clinically challenging patients.

Methods

We conducted a retrospective review of the clinical history and outcomes of 14 patients with treatment-refractory, severely disabling TS and psychiatric comorbidity (8 males; mean age: 21.8 years, range: 12-43) who underwent GPi-DBS combined with bilateral anterior capsulotomy in our hospital. At the time of surgery, patients presented mainly with obsessive-compulsive disorder and affective disorders. Clinical outcome assessments of tic and psychiatric symptoms, as well as of general adaptive functioning and quality of life, were performed at the time of surgery and at 6 months, at 12 months, and between 24 and 96 months after surgery.

Results

After surgery, all patients showed significant progressive improvements in tic and psychiatric symptoms along with improvements in general adaptive functioning and quality of life. At the final follow-up, patients were functionally recovered and displayed no or only mild tic and psychiatric symptoms. All patients tolerated the treatment reasonably well, with no complications or serious side effects.

Conclusions

GPi-DBS combined with bilateral anterior capsulotomy seems to offer major clinical benefits to patients with severely disabling and otherwise treatment-refractory TS and psychiatric comorbidity. Randomized controlled trials are warranted to assess the combined treatment under experimentally controlled conditions.

596 MR-guided Focused Ultrasound versus Radiofrequency Capsulotomy for Treatment-Refractory Obsessive-Compulsive Disorder: A Cost-Effectiveness Analysis

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Introduction

Meta-analytic techniques recently supported neuroablation as a promising therapy for treatment-refractory obsessive-compulsive disorder (OCD) with a more favorable complication rate than deep brain stimulation. Moreover, these pooled findings suggested that bilateral radiofrequency (RF) capsulotomy had marginally greater efficacy than unilateral ablation, stereotactic radiosurgery, and cingulotomy. MR-guided focused ultrasound (MRgFUS) capsulotomy is an emerging therapy for OCD, with preliminary data suggesting safety and efficacy. Thus, we sought to determine the cost and clinical parameters necessary for MRgFUS capsulotomy to be a viable alternative to RF capsulotomy.

Methods

We created a decision analytical model of MRgFUS with RF capsulotomy for OCD. Outcome parameters included percent surgical improvement in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, complications, and side effects. The analysis compared measured societal costs, derived from Medicare reimbursement rates, and effectiveness, based on published RF data. Theoretical risks of MRgFUS capsulotomy were based on published essential tremor outcomes. Sensitivity analysis yielded cost, effectiveness, and complication rate as critical MRgFUS parameters defining the cost-effectiveness threshold.

Results

Literature search identified eight publications (162 subjects). The average reduction of preoperative Y-BOCS score was 56.6% after RF capsulotomy, with a 22.6% improvement in utility. Complications occurred in 16.2% of RF cases. In 1.42% of cases, complications were considered acute-perioperative and incurred additional hospitalization cost. The adverse events in the other 14.8% of cases did not incur further costs, although they impacted utility. Rollback analysis of RF capsulotomy yielded an expected effectiveness of 0.212 QALYs/year at an average cost of $24,099. MRgFUS capsulotomy was more cost-effective under a range of possible cost and complication rates (Figure 1).

Conclusions

MRgFUS capsulotomy lacks many of the inherent risks associated with more invasive modalities and has potential to be a safe and cost-effective treatment for OCD. Future trials should directly assess outcomes for this emerging indication against established neurosurgical OCD therapies.

597 Connectivity Analysis of Cingulotomy Lesion Using Tractography: Do More Effective Targets Exist?

Jennifer A. Sweet; Suraj Thyagaraj; Curtis Tatsuoka; Jonathan P. Miller; Cameron C. McIntyre

Introduction

The cingulum bundle (CB) has been implicated in the pathophysiology of psychiatric disorders. Anatomic and radiographic CB connectivity analyses suggest that it is heterogeneous in composition, with certain regions, such as the rostral dorsal CB, having greater connectivity than others to cortical and subcortical structures associated with mood and thought, like the anterior cingulate cortex (ACC). Cingulotomy procedures for the treatment of depression, pain, and obsessive-compulsive disorder consist of 1-3 bilateral lesions in a portion of the dorsal ACC (dACC) and underlying CB, yet the exact region responsible for symptom relief is unclear. This study uses tractography to assess the connectivity of standard cingulotomy lesions, as well as of subdivisions of the rostral dorsal CB, to cingulate and non-cingulate structures involved in psychiatric disorders.

Methods

Healthy volunteers underwent T1- and diffusion-weighted MRIs. Region of interest (ROI) masks were created to replicate three cingulotomy lesions commonly used, and to make eight equally-sized subdivisions of the rostral dorsal CB (Figure1). Deterministic tractography was performed, and the connectivity of each ROI to 11 cortical/subcortical brain structures was assessed.

Results

Five subjects were included. All cingulotomy lesions showed greatest connectivity to the dACC, followed closely by the posterior cingulate cortex (PCC) and dorsomedial frontal cortex (dmFC) for lesion 1, and the dmFC for lesions 2 and 3 (Table1). The CB subdivisions with highest connectivity to the dACC were 4-5, and those to the dmFC were 3-4 (Table2). Thus, the antero-rostral-most portion of the CB showed greatest connectivity to key brain structures, including the dACC and dmFC.

Conclusions

Using deterministic tractography, a connectivity analysis of cingulotomy lesions and CB subdivisions was performed. The greatest connectivity between all cingulotomies was to the dACC and dmFC. However, the CB subdivisions with highest connectivity to these regions were located antero-rostrally, possibly suggesting a more effective surgical target for psychiatric diseases.

598 Deep Brain Stimulation of the Bilateral Habenula: Targeting and Applications

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Introduction

The habenula (Hb) is an epithalamic structure located at the center of the dorsal diencephalic conduction system. Imaging of the habenula is critical due to its role in psychiatric disorders associated with dysregulated reward circuitry function relevant to mood disorders, and substance use disorders. However, in vivo neuroimaging research targeting the human habenula has been limited by its small size and low anatomical contrast which limits the therapeutic clinical potential of targeting the structure with neuromodulation.

Methods

Conventional T1-weighted magnetic resonance imaging (MRI) at 3Tesla shows excellent contrast of cortical gray white matter with Quantitative Susceptibility Mapping (QSM) providing further contrast in iron-rich deep gray matter. We used (QSM)/T1-w hybrid image generation to view the Hb, and then use habenular Deep Brain Stimulation(DBS) for 4 patients who suffered from treatment refractory unipolar major depression, bipolar disorder with treatment refractory depression, or obsessive compulsive disorder.

Results

The hybrid image preserves both the enhanced anatomical contrast of deep brain nuclei in the susceptibility map and clear cortical structures defined in the T1-weighted image. In the follow up (2-6 month) of post habenular DBS, most patients experienced symptom improvement without severe side effects.

The hybrid image preserves both the enhanced anatomical contrast of deep brain nuclei in the susceptibility map and clear cortical structures defined in the T1-weighted image. In the follow up (2-6 month) of post habenular DBS, most patients experienced symptom improvement without severe side effects.

Conclusions

This research shows that (QSM)/T1-w hybrid image generation can allow Hb identification, and that its stimulation may benefit some patients with unipolar, bipolar disorder with treatment refractor depression, or obsessive compulsive disorder.

599 Controlling Positive Symptoms of Schizophrenia Through Deep Brain Stimulation (DBS) of the Ventral Tegmental Area

Juan A. Barcia Blanca Reneses, Cristina Nombela, Julia García-Albea, , Bryan Srange

Introduction

Schizophrenia animal models have shown that the ventral tegmental area (VTA) is hyperactive, and this is correlated with the appearance of positive symptoms. We hypothesized that stimulating the VTA with DBS at tonic frequencies (3,5 Hz) would pacemake the VTA, avoiding spontaneous bursts and providing a correct basal level of DA at the frontal cortex, thus improving the positive symptoms during the psychotic episodes.

Methods

A 39 years old married male diagnosed with schizophrenia since he was 19 underwent Deep brain stimulation (DBS) surgery targeting at bilateral VTA. After a pilot study were 11 different stimulation parameters were evaluated with the same patient, 4 set of patterns were selected and tested for 1 month each followed by 1 week wash-out. Psychiatric (PANSS, CGI and GAF scales) and neuropsychological assessment were carried out at the end of each period. A PET scan and a DAT scan was conducted pre and post surgery.

Results

The patient presented a reduction of 58,62% in the PANSS positive, 26,08% in the PANSS negative, 30 points reduction at the GAF and from 6 to 5 at ICG under 6Hz at the left VTA stimulation. Such stimulation was not accompanied by neuropsychological side effects. After long-term stimulation (1 year) based on such parameters (left sided 3,5 Hz) and some medication adjustment, the patient maintained the benefit in his symptoms.

Conclusion

We report a case of a schizophrenic patient resistant to medication in whom stimulation of the left VTA at improved the psychotic symptoms, with a great distance from the delusional activity, permitting him to return to a better daily activity.