S2D.03

WIRELESS DEEP BRAIN STIMULATION IN FREELY MOVING MICE WITH NONRESONANT POWERING OF MAGNETOELECTRIC NANOPARTICLES

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Abstract

Devices that electrically modulate the deep brain have enabled important breakthroughs in the management of neurological and psychiatric disorders. Such devices are typically centimeter-scale, requiring surgical implantation and wired-in powering, which increases the risk of hemorrhage, infection, and damage during daily activity. Recently, several remotely powered devices have emerged that could enable less invasive neuromodulation. The most clinically promising of these do not rely on transgenesis of neural tissue, but instead directly create electric signals to achieve neuromodulation. However, it has not yet been possible to scale down such devices sufficiently to enable complete implantation in the brain while still achieving deep-brain neuromodulation. Herein, we present injectable, magnetoelectric nanoelectrodes that wirelessly transmit electrical signals to the brain in response to an external magnetic field. Importantly, this mechanism of modulation requires no genetic modification of neural tissue and allows animals to freely move during stimulation. Using these nanoelectrodes, we demonstrate neuronal modulation in vitro and in deep brain targets in vivo. We also show that local thalamic modulation promotes modulation in other regions connected via basal ganglia circuitry, leading to behavioral changes in mice. This work demonstrates the potential of magnetoelectric materials as nanoelectrodes for wireless electrical modulation of deep brain targets. Herein, we have shown that we can stimulate Magnetoelectric Nanoparticles (MENPs) with a magnetic field to remotely generate electric polarization of the MENPs. We have shown evidence that non-resonant frequency magnetic stimulation of MENPs locally modulates neuronal activity in vitro and in vivo. We have also demonstrated that this modulation is sufficient to change animal behavior and to modulate other regions of the cortico-basal ganglia-thalamo-cortical circuit. Future work will be key to optimizing magnetoelectricity based neural devices and understanding the abilities and limitations of this technology. Magnetoelectric materials present a versatile platform technology for less invasive, deep brain neuro-modulation.

S2D.04

REMODELY CONTROLLED MAGNETIC STIMULATION WITH LOCALIZED CHEMICAL RELEASE

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Abstract

For the rodent models, whose behavior is sensitive to the implanted foreign objects, investigation of the neural circuits underlying their abnormal behavioral phenotypes via invasive optogenetic and electrical neuromodulation devices poses a challenge. Here we developed a remotely controlled strategy for magnetothermal deep brain stimulation of genetically identifiable neural populations in freely moving rodents. This approach enabled temporally and spatially precise chemical manipulation of neural activity by local release of designer drugs in response to remote exposure to alternating magnetic fields. We achieved the implant-free convenience of magnetothermal neuromodulation concomitantly with the genetic precision of chemogenetics, and thus enabled spatial and temporal modulation for behavioral investigation. We anticipate that the magnetochemogenetic tools will facilitate investigation of neural circuits during behavioral experiments and enable neuromodulation studies in rodent models incompatible with permanently implanted hardware.

Keywords: magnetic stimulation, chemical delivery, neuromodulation
Abstract

Background: Navigated repetitive transcranial magnetic stimulation (nrTMS) is effective therapy for stroke patients. Neurorehabilitation could be supported by low-frequency stimulation of the non-damaged hemisphere to reduce transcallosal inhibition.

Objective: The present study examines the effect of postoperative nrTMS therapy of the unaffected hemisphere in glioma patients suffering from acute surgery-related paresis of the upper extremity (UE) due to subcortical ischemia.

Methods: We performed a randomized, sham-controlled, double-blinded trial on patients suffering from acute surgery-related paresis of the UE after glioma resection. Patients were randomly assigned to receive either low frequency nrTMS (1 Hz, 15 minutes) or sham stimulation directly after glioma resection. Patients were randomly assigned to receive either low frequency nrTMS (1 Hz, 15 minutes) or sham stimulation directly before physical therapy for 7 consecutive days. We performed primary and secondary outcome measures on day 1, on day 7, and at a 3-month follow-up (FU). The primary endpoint was the change in Fugl-Meyer Assessment (FMA) at FU compared to day 1 after surgery.

Results: Compared to the sham stimulation, nrTMS significantly improved outcomes between day 1 and FU based on the FMA (mean [95% CI] +31.9 [22.6, 41.3] vs. +4.2 [-4.1, 12.5]; P = 0.001) and the National Institutes of Health Stroke Scale (NIHSS) (-5.6 [-7.5, -3.6] vs. -2.4 [-3.6, -1.2]; P = 0.02). To achieve a minimal clinically important difference of 10 points on the FMA scale, the number needed to treat is 2.19.

Conclusion: The present results show that patients suffering from acute surgery-related paresis of the UE due to subcortical ischemia after glioma resection significantly benefit from low-frequency nrTMS stimulation therapy of the unaffected hemisphere.

Keywords: Glioma, Surgery, Subcortical Ischemia, Rehabilitation

S2E.03

SLEEP-LIKE CORTICAL BISTABILITY AFTER FOCAL AND MULTIFOCAL BRAIN LESIONS

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Abstract

The neural mechanisms responsible for loss and recovery of function after brain injury are still elusive. Recently, by combining navigated Transcranial Magnetic Stimulation with electroencephalography (TMS-EEG) we have tested the hypothesis that cortical bistability, a basic neurophysiological phenomenon of sleep characterized by the occurrence of neuronal silences (OFF-periods), is a key neuronal mechanism underlying loss of function after brain injury. First, we have shown that the occurrence of cortical OFF-periods in unresponsive, severely brain-injured patients may be the main determinant in preventing the build-up of complex brain interactions, which are a prerequisite for consciousness to emerge (Rosanova et al., Nat Comm 2018).

These results have been then replicated and extended by performing TMS-EEG measurements in patients affected by focal brain-injuries (Sarasso et al., Brain 2020) in which they revealed the occurrence of sleep-like OFF-periods in the area surrounding the lesion. Interestingly, these perilesional sleep-like responses to TMS were associated with a local disruption of complexity. Since the mechanisms of OFF-periods are well known at the cellular level and potentially reversible, these findings overall suggest that sleep-like cortical bistability may have major potential implications for developing novel readouts and treatments to foster recovery of function after brain injury.

[NS: Part of the symposium Navigated TMS - based techniques in rehabilitation of motor function: diagnostics, prognostics, therapy (ID: 14)]

Keywords: TMS, EEG, Consciousness, Complexity, Cortical bistability

S2E.04

THE CORTICOSPINAL RESERVE: SURGICAL DECOMPRESSION RESTORES CORTICAL MOTOR EXCITABILITY AND FUNCTION IN CASES OF MILDLY SYMPTOMATIC DEGENERATIVE CERVELICAL MYELOPATHY

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Abstract

Background: We have recently shown an adaptive reorganization of the corticospinal network in patients with degenerative cervical myelopathy (DCM) which led to the concept of the ‘corticospinal reserve capacity’. In patients suffering from mild symptoms (JOA>12) and preserved reserve an increased neuronal recruitment and disinhibition with enlarged motor area was observed. In contrast, severely symptomatic patients (JOA<12) with an exhausted reserve presented with a reduced motor area, reduced corticospinal conductivity and increased inhibition. The current prospective multicenter trial has been designed to validate the new pathophysiological concept.

Methods: 120 patients with DCM from four spine centers in Germany and Switzerland were examined preoperatively and 9 months after surgical decompression with navigated transcranial magnetic stimulation (nTMS). Corticospinal excitability was determined by navigated transcranial magnetic stimulation (nTMS) with an elevated RMT (p<0.05; RC prep 9.2±5.0 vs. follow up 11.2±5.4 p<0.05) and a favorable functional outcome (JOA prep 14.0±1.1 vs. JOA follow up 14.5±1.5). In contrast, patients with severe symptoms (JOA<12) presented a reduced excitability of cortico-cortical axons reflected by an elevated RMT (p<0.05; JOA<12: 43.8±11.4 vs. JOA ≥12: 39.2±8.4) and a reduced RC slope (p<0.05; JOA<12: 8.4±4.8 vs. JOA 15-17: 11.1±5.2).

Conclusions: In summary our prospective multicenter trial confirmed our concept for functional reorganization in patients suffering from DCM, i.e. the ‘corticospinal reserve capacity’. This innovative approach to evaluate patients suffering from DCM might improve current concepts of clinical diagnostics and impact future treatment strategies.

Keywords: TMS, cervical myelopathy, cortical reorganization

S2F.01

STIMULATION EVOKED POTENTIALS FOR OPTIMAL PHYSIOLOGICAL TARGETING OF SUBCALLOSAL CINGULATE FOR DEPRESSION

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Abstract

The cortical evoked response to single pulses of deep brain stimulation of a white matter target provides a critical extension of tractography-guided treatment optimization. On the level of individuals, the stimulation evoked potential (EP) may serve as a read-out to confirm optimal target engagement (i.e., location of implant, therapeutic dose selection) relative to white matter architecture. A critical next step in developing this application is to identify variance in the SCC EP that accounts for individual differences in white matter perturbation. In this presentation, we review putative features of the SCC DBS EP, including a posterior deflection (p100), which arcs from SCC to the posterior midline and may reflect perturbation of cingulum bundle; and an anterior feature (p40) that implicates forceps minor, which innervates medial frontal cortex. We describe the advantages of pairing invasive neuromodulation with non-invasive recording of cortical electrophysiology (256-array) and present results from patients (n=12) undergoing SCC DBS for to treat depression. EPs were recorded from each of 8 contacts (4 per hemisphere) and at varying doses. Patient-specific tractography models provided an estimate of white matter structure, which was then regressed on features of the evoked potential. Preliminary results suggest a relationship between the p40 peak amplitude (i.e., location of implant, therapeutic dose selection) relative to white matter architecture. A critical next step in developing this application is to identify variance in the SCC EP that accounts for individual differences in white matter perturbation. In this presentation, we review putative features of the SCC DBS EP, including a posterior deflection (p100), which arcs from SCC to the posterior midline and may reflect perturbation of cingulum bundle; and an anterior feature (p40) that implicates forceps minor, which innervates medial frontal cortex. We describe the advantages of pairing invasive neuromodulation with non-invasive recording of cortical electrophysiology (256-array) and present results from patients (n=12) undergoing SCC DBS for to treat depression. EPs were recorded from each of 8 contacts (4 per hemisphere) and at varying doses. Patient-specific tractography models provided an estimate of white matter structure, which was then regressed on features of the evoked potential. Preliminary results suggest a relationship between the p40 peak amplitude (i.e., location of implant, therapeutic dose selection) relative to white matter architecture. A critical next step in developing this application is to identify variance in the SCC EP that accounts for individual differences in white matter perturbation. In this presentation, we review putative features of the SCC DBS EP, including a posterior deflection (p100), which arcs from SCC to the posterior midline and may reflect perturbation of cingulum bundle; and an anterior feature (p40) that implicates forceps minor, which innervates medial frontal cortex. We describe the advantages of pairing invasive neuromodulation with non-invasive recording of cortical electrophysiology (256-array) and present results from patients (n=12) undergoing SCC DBS for to treat depression. EPs were recorded from each of 8 contacts (4 per hemisphere) and at varying doses. Patient-specific tractography models provided an estimate of white matter structure, which was then regressed on features of the evoked potential. Preliminary results suggest a relationship between the p40 peak amplitude (i.e., location of implant, therapeutic dose selection) relative to white matter architecture. A critical next step in developing this application is to identify variance in the SCC EP that accounts for individual differences in white matter...