Table 1
Aggregating data over the same task may produce a significant summary effect.

Task	Figure/Table in the article	SMD (95% CI)	*Z* value	*P* value
Stop signal task	Fig. 1B–E/Table 1, 2	−0.39 (−0.68, −0.11)	−2.69	0.007
Stop signal task (SSRT only)	Fig. 1C–E/Table 1, 2	−0.37 (−0.69, −0.05)	−2.26	0.024
Stroop task	Fig. 1F–G/Table 2	0.51 (−0.01, 1.03)	1.92	0.055
Verbal fluency	Fig. 2C–D/Table 4	0.26 (0.00, 0.53)	1.94	0.052

To summarize, results from meta-analyses should be interpreted cautiously. Attention must be paid to the study inclusion criteria, selection of outcome measures, the method of data synthesis and calculation of the effect size.

Acknowledgments

We would like to thank Drs. James Sawers and Ilya Lipkovich for their generous input to the manuscript.

Drs Pratik Chhatbar and Wuwei Feng are both supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM109040. Dr. Feng is also supported by American Heart Association (14SDG1829003).

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Received 7 May 2015

http://dx.doi.org/10.1016/j.brs.2015.06.001

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The Use of Stimulation Field Models for Deep Brain Stimulation Programming

Introduction

Computational models of deep brain stimulation (DBS) have proven useful for predicting and visualizing its effects on a patient-specific basis. The creation and development of these types of models has followed a roughly ten-year time span from initial feasibility assessment to integration into clinical decision support tools. Specifically, we have focused much of our effort on the development of biophysically-based estimators for stimulation spread, or the volume of tissue activated (VTA), which are also known as stimulation field models (SFMs) in the GUIDE system from Boston Scientific. These models are now entering a new phase in which their utility is being assessed not only for scientific analysis on the effects of DBS, but also to facilitate the selection of stimulation parameters in DBS patients with pulse generators that are growing more complex. We anticipate that the need for these types of programming tools will continue to evolve as stimulation systems incorporate new features and as indications for DBS expand. Therefore, the purpose of this letter is to provide a succinct review of the development and translation of these models into DBS clinical practice, as well as an overview of how we suggest that clinical users interpret the VTA/SFM.

Computational models of DBS

Initial computational studies were conducted to answer the question: is it feasible to predict the effects of DBS using patient-specific models? These models are constructed using two tightly integrated numerical approaches. First, finite element models (FEMs) are solved for the electric field generated by the DBS electrode. FEMs of DBS have been solved using the Poisson equation, which calculates the voltage distribution in the brain as a function of the source type (voltage- or current-controlled DBS), electrode geometry, stimulation waveform and tissue conductivity. FEMs can also account for inhomogeneous and anisotropic tissue conductivities of the human brain tissue surrounding the implanted electrode. The second major modeling component is the use of multicompartmental neuron models which are coupled to the electric field models to simulate the neural response to stimulation [7]. Experimentalists from 1960s to 1970s established that the primary effect of extracellular electrical stimulation in the central nervous system (CNS) was the generation of action potentials in axons [11]. Therefore, our focus has long been on characterizing the axonal response to DBS. The VTA/SFM is constructed by identifying axons that are suprathreshold for activation by the DBS-induced electric field, and represent a region where brain tissue is likely to be directly modulated by DBS. It is important to note that VTA/SFMs are constructed with highly excitable myelinated axons, such that their size for a given set of stimulation parameter settings represents an intentionally large prediction. This design choice was made because in most DBS applications, therapeutic stimulation can be applied in a target region with some degree of flexibility, but stimulation spread into side effect areas is more sensitive. In turn, a major goal of the VTA/SFM is to help avoid unintentional overstimulation of the patient and subsequent stimulus spread into side effect areas.

The size of the VTA/SFM is strongly dependent on the amount of charge delivered during each stimulation pulse; increases in

amplitude or pulse width each increase the size of the VTA/SFM. Conversely, a robust foreign body reaction can decrease the size of the VTA/SFM by creating a large voltage drop across the encapsulation layer. The thickness of the encapsulation layer can be predicted from the DBS electrode contact impedance. Hence, the size of the VTA/SFM is dependent on several key attributes of the DBS device and brain biophysical properties.

Accuracy of model predictions

Once the feasibility of patient-specific DBS models was established, a natural next question was considered: are the model predictions accurate? To assess this we used both direct and indirect measurements. Model predictions of the voltage distribution in the brain during DBS were validated by *in vivo* recordings in a non-human primate [8]. Model predictions of the VTA/SFM were indirectly validated by detecting stimulation-induced side effects such as STN DBS-induced activation of the corticospinal tract [3,5]. These experiments and others provided evidence to demonstrate the accuracy of the modeling approach.

An additional consideration with regard to accuracy is image registration. Many DBS targets show poor contrast on conventional, clinical MRI acquisitions. Therefore an atlas registration is performed in order to determine lead location relative to anatomical structures such as the STN. This is a common procedure that is performed not only for VTA/SFM visualization but also during stereotactic DBS surgical planning. While there are many different approaches to image registration, there is no gold standard for determining accuracy. Our approach to this problem has consistently been to maximize registration accuracy in the region around the DBS lead, and to use stereotactic microelectrode recording data when available as additional constraints in the registration process.

Overall, the accuracy of these model predictions is based on judicious selection of many variables. Some can be characterized with a high degree of certainty (e.g. the parameters of the stimulation waveform), while others have several potential sources of variability and uncertainty (e.g. tissue properties or the encapsulation layer). The major conclusion from these validation studies was that the models are sufficiently accurate to assist in clinical decision making, as discussed in the following sections.

Clinical translation of DBS models

Clinical studies have provided evidence that using DBS models can improve patient outcomes [6] and reduce the amount of time necessary for programming [4,10]. In addition, a clinical trial was recently funded (NIH R01 NR014852, PIs: Butson & Okun) during which nurses will use DBS models to program Parkinson's disease patients in their homes. We believe that these models can provide improvements for two reasons. First, the models are provided to clinicians in simple, interactive software tools that are amenable to a clinical workflow. Second, by virtue of having a simple interface clinicians are able to focus on the information content embodied in the model. Specifically, they were able to use visual feedback from the VTA/SFMs and their overlap with nearby anatomical nuclei to augment information gathered during patient exams. Importantly, we do not anticipate that the use of VTA/SFMs will obviate the need for motor exams or supplant good clinical judgment. Rather, we anticipate that their use will augment the information available to practitioners, and allow them to focus more energy on the neurological objectives of stimulation.

The future of DBS programming

Indications for DBS are expanding; a search of clinicaltrials.gov lists 178 trials that are currently open as of 2015. Additionally, new device technologies are becoming available such as current-controlled stimulation with multiple independent sources and advanced DBS electrode contact designs. As DBS systems grow more complex, and as the potential indications for DBS are expanding, there is a growing need for clinical decision support systems to assist device programmers in the selection of optimal stimulation parameters. For example, both computational and *in vivo* studies suggest that directional electrodes can provide preferential activation on one side of the DBS lead [9]. Further, these lead designs can be combined with novel stimulation patterns to achieve greater selectivity than can be achieved with cylindrical electrode contacts [2]. These innovations and others have the potential to improve outcomes, but only if they can be quickly and effectively applied by practitioners.

Our experience has been that introducing new technology into clinical practice can change behavior in unexpected ways. For example, while many patients have been traditionally programmed with monopolar settings (i.e. one electrode contact as the cathode and the IPG case as the anode), the use of interactive VTA/SFMs with multiple independent current sources has allowed the titration of stimulation across up to four contacts, each of which was hypothesized to affect different anatomical targets [1]. These changes in behavior are most likely attributable to a difference in the type of feedback provided during DBS programming. Traditionally, stimulation settings are titrated based on immediate feedback either from the patient or the clinician's examination. In contrast, the use of VTA/SFMs allows the clinician to visually explore how the selection of stimulation settings interacts with nearby anatomical structures. Using this process clinicians could avoid stimulating regions that are likely to cause side effects, and instead focus on a subset of stimulation settings that are likely to be therapeutically effective. This type of visual review can be performed much more quickly than the traditional programming process, and could be especially useful when treating symptoms that are responsive to DBS but do not have an acute response to changes in stimulation settings. Hence, we anticipate that the usage of these models will continue to evolve, and in turn the information gathered during usage can expand our body of knowledge about how to best titrate DBS settings for future patients. Lastly, these visual programming systems provide a platform for future integration of new imaging information as it becomes available. Advances in imaging are now providing information in the form of tractography, functional connectivity and improved contrast in anatomical imaging, potentially allowing direct targeting of structures that previously showed little contrast on clinical MRI acquisitions.

Disclosures and Conflicts of Interest: CRB and CCM have authored intellectual property related to the content of this letter. CRB has served as a consultant for Boston Scientific, St Jude Medical, NeuroPace, Intelect Medical, Advanced Bionics and Functional Neuromodulation. CRB is a shareholder of Intelect Medical. CCM is a paid consultant for Boston Scientific Neuromodulation, and is a shareholder in the following companies: Surgical Information Sciences, Inc.; Autonomic Technologies, Inc.; Cardionomic, Inc.; Neuros Medical, Inc.

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Received 5 May 2015

http://dx.doi.org/10.1016/j.brs.2015.06.005

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A Double-blind, Placebo-controlled Study of the Effects of Daily tDCS Sessions Targeting the Dorsolateral Prefrontal Cortex on Tinnitus Handicap Inventory and Visual Analog Scale Scores

Dear Editor,

Tinnitus is a common condition that affects approximately 20.7% of the general population, according to a recent study [1]. Although different causes may be at play, a likely pathophysiological mechanism might be, for example, maladaptive reorganization of the auditory cortex in response to cochlear damage or degeneration and auditory loss restricted to specific sound frequencies. The persistence of continuous neural activity in the corresponding tonotopic cortical representation areas might, then, cause phantom perception of sound in the affected frequencies, leading to tinnitus. In fact, it has been shown that tDCS targeting the auditory cortex is capable of transiently modulating tinnitus intensity [2].

However, the affective and emotional aspects of tinnitus perception may be very important to the degree of patient discomfort, irrespective of tinnitus intensity. Approximately one-third of patients report moderate to severe tinnitus-related annoyance [1]. Since tDCS targeting the dorsolateral prefrontal cortex (DLPC) has already been shown to modulate depression and other neuropsychiatric symptoms [3–5], a few studies have explored possible effects of tDCS on subjective tinnitus-related discomfort and annoyance [6]. Vanneste et al. [7] reported that one session of bilateral DLPC tDCS had an acute tinnitus-suppressing effect, but only with a right anode-left cathode montage. Frank et al. [8] found that 6 sessions of tDCS targeting the DLPC decreased perceived discomfort due to tinnitus, but did not significantly change Tinnitus Handicap Inventory (THI) scores. In that study, patients received tDCS twice a week. Faber et al. [9] also performed a study with two tDCS sessions per week. All other studies published to date have measured tinnitus discomfort and intensity before and after single sessions of tDCS [6]. It is conceivable, therefore, that a daily stimulation protocol, as has been proposed for the treatment of depression and chronic pain [10], could result in a cumulative and significant effect of tDCS sessions targeting the DLPC on THI and VAS scores.

Here, we report a study of two groups of tinnitus patients carried out with a double-blind, placebo-controlled design, to test the hypothesis that 5 consecutive daily sessions of tDCS targeting the DLPF could have a significant effect upon THI and VAS scores.

Eighteen patients with chronic tinnitus were enrolled in this study after giving written, informed consent. Nine men and 9 women, ages 45–70 (mean 54.72) participated in the study. Mean tinnitus duration was 12.86 years (range: 1–30 years).

All patients had sensorineural hearing loss, which was bilateral in nine. Patients with a history of seizures, suspected organic brain damage, depression, as well as patients with cardiac pacemakers, pregnant women and those taking medications acting on the central nervous system were excluded.

All tDCS sessions were performed at the Neuromodulation Laboratory, Psychiatry Unit, University of Brasília Hospital, Brasília, Brazil. The experimental protocol was approved by the local Ethics Committee.

Patients were randomly assigned to either a real tDCS or a sham procedure group. All patients underwent 5 daily consecutive tDCS sessions. Visual analog scale (VAS) and Tinnitus Handicap Inventory (THI) scores were recorded before and after treatment.

tDCS was delivered by an Endophasys D® stimulator (KLD Instruments, São Paulo, Brazil) through electrodes embedded in sponges (area: 35 cm^2) soaked with NaCl 0.9%. The cathode was placed over the left dorsolateral prefrontal cortex (DLPFC) with the center over F3 (10–20 system), and the anode over the right DLPFC (F4). Stimulation was performed at 2.0 mA over 20 min (10 s ramp-in and ramp-out each). During the sham procedure, there was also a ramp-in period of 10 s, after which the current was turned off for the remainder of the session, in order to cause the same ramp-in sensations experienced by the real tDCS group.

The procedure was well tolerated by all subjects, with no untoward effects.

Statistical analysis was performed with the Kruskal–Walis Test, in order to verify if there were significant interactions between VAS and THI scores, real tDCS and sham tDCS. The Wilcoxon signed-rank test was used to compare the real and sham treatment groups, as well as VAS and THI scores before and after treatment. There