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The Role of Electrode Location and Stimulation Polarity in Patient Response to Cortical Stimulation for Major Depressive Disorder

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ABSTRACT

Background: Major depressive disorder (MDD) is a neuropsychiatric condition that affects about one-sixth of the US population. Chronic epidural stimulation (EpCS) of the left dorsolateral prefrontal cortex (DLPFC) was recently evaluated as a treatment option for refractory MDD and was found to be effective during the open-label phase. However, two potential sources of variability in the study were differences in electrode position and the range of stimulation modes that were used in each patient. The objective of this study was to examine these factors in an effort to characterize successful EpCS therapy.
Methods: Data were analyzed from eleven patients who received EpCS via a chronically implanted system. Estimates were generated of response probability as a function of duration of stimulation. The relative effectiveness of different stimulation modes was also evaluated. Lastly, a computational analysis of the pre- and post-operative imaging was performed to assess the effects of electrode location. The primary outcome measure was the change in Hamilton Depression Rating Scale (HDRS-28).
Results: Significant improvement was observed in mixed mode stimulation (alternating cathodic and anodic) and continuous anodic stimulation (full power). The changes observed in HDRS-28 over time suggest that 20 weeks of stimulation are necessary to approach a 50% response probability. Lastly, stimulation in the lateral and anterior regions of DLPFC was correlated with greatest degree of improvement.
Conclusions: A persistent problem in neuromodulation studies has been the selection of stimulation parameters and electrode location to provide optimal therapeutic response. The approach used in this paper suggests that insights can be gained by performing a detailed analysis of response while controlling for important details such as electrode location and stimulation settings.

Introduction

Nearly 16% of the American population suffers from depression over their life time [1,2]. Major depressive disorder (MDD) is a neuropsychiatric condition that is characterized by the World Health Organization (WHO) as a leading cause of disability worldwide [3]. In addition to affecting quality of life, it is a major cause of suicide and contributes to the prevalence of associated comorbid disorders like diabetes and cardiovascular disease [4]. The efficacy of pharmacological treatments and psychotherapy is varied for treating this population. Therefore, other treatment options have been evaluated including neuromodulation therapy [5–7].

The dorsolateral prefrontal cortex (DLPFC) is a potential target for neuromodulation therapy. Neuropsychological and neuroimaging

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studies have found the DLPFC to be functionally involved in mood disorders [8,9]. More specifically, the left dorsolateral prefrontal cortex (L-DLPFC) (Brodmann areas 9/46) has been found to be hypoactive in individuals suffering from MDD [8,10]. Neuromodulation [11] interventions such as cortical stimulation [6,12,13] and repetitive transcranial magnetic stimulation [14,15] (rTMS) have targeted the L-DLPFC for MDD [7]. Chronic epidural stimulation (EpCS) of the L-DLPFC was recently evaluated in an 11 patient safety and feasibility study [5]. This method is considered safer than techniques such as deep brain stimulation [4,16] (DBS) because it does not require penetration of the dura. It is also considered more focal than TMS or vagal nerve stimulation (VNS) [6] because the electrodes are located directly adjacent the neuroanatomical target region.

A wide range of stimulation configurations are available for EpCS. These can strongly affect the strength and orientation of the induced electric field as well as the specificity of the neurons that are recruited [6]. The stimulation parameters (frequency, amplitude, pulse width) and the electrode contact locations are expected to be cofactors for the overall effectiveness of the treatment. In general, cathodal stimulation decreases cortical excitability and reduces spontaneous firing by hyperpolarizing the underlying neurons. Conversely, anodal stimulation is believed to have the opposite effect by depolarizing the underlying neurons [17,18]. The orientation of the dendrites and axons in the induced electrical field further influence the direction of the polarizing effect. In a simulation study of EpCS applied at the motor cortex, it was determined that a cathode excites fibers that are parallel while an anode excites fibers that are perpendicular to the surface of the lead [18,19]. These orientations are highly correlated with a specific location on the cortical surface. An rTMS study [15] for depression over the prefrontal cortex was conducted to validate the differential effects of location within the DLPFC. They found a linear relationship between coil placement and Hamilton Depression Rating scale [20] (HDRS-28) improvement [15]. These findings illustrate the complexity associated with EpCS and the treatment of depression in terms of electrode location and stimulation protocol.

A recent study reported on the feasibility of EpCS of L-DLPFC for the treatment of MDD in 11 patients treated at three sites [5]. In this paper the data from the previous study were analyzed further to understand the degree to which stimulation parameters and electrode location were predictors of clinical response. The objective was to estimate the degree of variability in HDRS-28 that is attributable to changes in stimulation protocol. In particular, the goals of this study were: 1) Determine whether changes in the stimulation protocol, which consisted mainly of varying anode/cathode configurations, had a differential effect on HDRS-28, 2) Estimate the time necessary for treatment to elicit a robust clinical response, 3) Explore the effects of stimulation location on clinical outcome.

Methods

Participants

Data from 11 subjects with recurrent MDD without psychotic features (6 male, 5 female) were analyzed. The inclusion criteria for these patients have been described in a previous report [5]. Approval from the Institutional Review Board at the Medical College of Wisconsin was obtained prior to conducting the analysis.

Study design

Participants were randomly assigned to either 8 weeks of an initial sham period ($n = 5$) or active stimulation ($n = 6$). Patients in the sham group received active stimulation after the initial 8 week period. The stimulation study duration was 104 weeks with periodic assessments using HDRS-28 (primary outcome), and the following secondary outcomes: Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment of Functioning (GAF), and Quality of Life Enjoyment and Satisfaction Questionnaire (QLES). For the present analysis, only the HDRS-28 scores were used.

Stimulation was applied using a two-electrode implantable paddle with platinum-iridium contacts in the L-DLPFC. Electrode contacts were 3.75 mm in diameter and 15 mm apart. They were implanted over the posterior half of the middle frontal gyrus. The implantable pulse generator (IPG), which was implanted in the subclavicular region, delivered continuous stimulation as specified by the stimulation protocol. Patients received repeated clinical evaluation during the study period. Clinical response was defined as 40% improvement from baseline HDRS-28 scores. Remission was defined as an HDRS-28 score of less than 10.

Stimulation settings

The IPG used in this study was capable of providing a range of stimulation modes that differed in polarity (anode or cathode), duty cycle (percentage of pulses that were active) and number of active contacts (one or two). Eight different stimulation modes were applied during the study. Each patient began with monopolar, anodal stimulation at 50 Hz, 150 μs pulse width (PW) and 6.5 mA of total current. The first stimulation mode applied was Q03. In this mode both the anterior and posterior electrodes were anodic and the current was divided between them (3.25 mA at each electrode). All patients were stimulated using this mode for the first 8 weeks of active stimulation. If this mode was effective, then other modes at reduced power were tried. First, modes Q29 (50% duty cycle of Q03) or Q28 (25% duty cycle of Q03) were tried to preserve effectiveness while simultaneously prolonging IPG battery life. If these modes failed to show an improvement, then the patient was switched to mode Q21, which provided unipolar stimulation where the polarity was toggled between anode and cathode in a pseudorandom manner. During this mode, the output polarity was set to one of the four unipolar configurations every second where either electrode could be anodic, cathodic or off. Because only one of the leads was active, all the current (6.5 mA) was delivered through the active electrode contact. Similar to Q03, if this mode was effective then the patient was switched to a lower power setting with mode Q37 (50% duty cycle of Q21) or Q36 (25% duty cycle of Q21) in an effort to extend IPG battery life. If none of these modes were effective, the clinician selected another appropriate setting. During the study, modes Q09 (75% duty cycle) and Q12 (50% duty cycle) were administered occasionally. Both of these were characterized as anodic stimulation modes at decreased power. All modes were categorized in three groups: anodic full power (Q03), anodic reduced power (Q28, Q29, Q09, Q12), and mixed polarity (Q21, Q36, Q37).

Data analysis

A cumulative incidence curve was calculated using the Kaplan–Meier survival algorithm to characterize the time necessary to observe a clinical effect of the treatment. The effect of stimulation mode on HDRS-28 over time was modeled via a piecewise linear mixed model. The baseline score and the slope of the change in HDRS-28 during each intervention mode (anodic full power, anodic reduced power, and mixed polarity) were included both as fixed and random effects. Thus, we could estimate the average over subjects while allowing for between-subject variability and incorporation of repeated measurements per

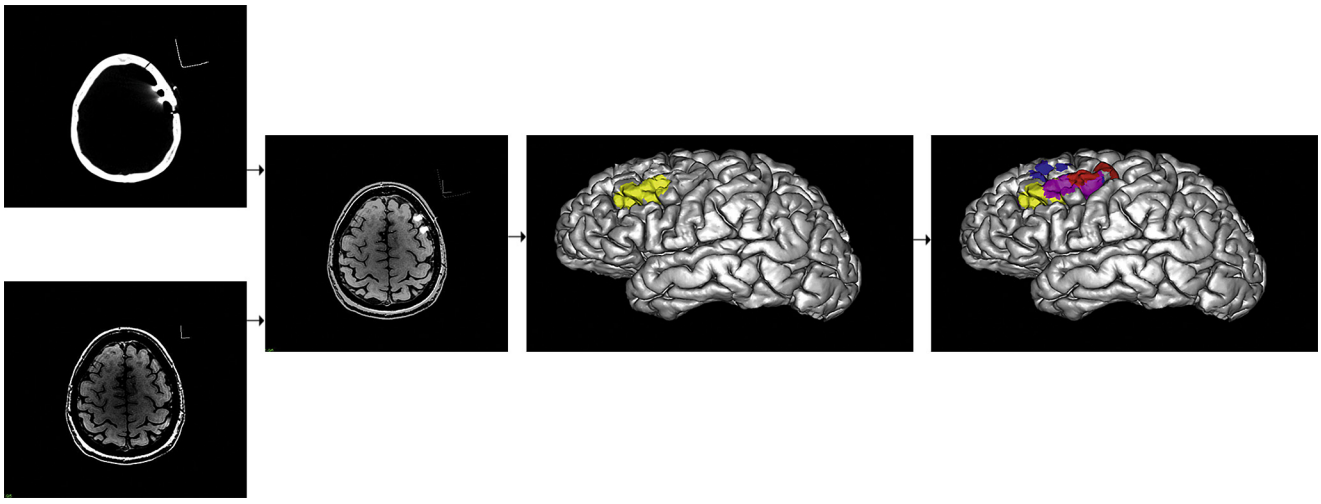

Figure 1. A flowchart describing the process used to determine the stimulation location. Imaging data for 4 subjects that were enrolled at the Medical College of Wisconsin were used to assess the effect of location on clinical outcomes. The pre-surgery MRI and post-surgery CT scans were co-registered to determine the site of implanted electrodes. The pial surface for each subject was then extracted via Freesurfer (Martinos Center for Biomedical Imaging). The stimulated region of interest (ROI) was defined as a locus of points on the pial surface within a 1-cm radius of each electrode. Each patient ROI was then mapped to one patient brain for comparison.

subject. The change-points of the model were not estimated; the subject-specific times of mode change were used instead. The model was fitted using Proc Mixed in SAS 9.2 (SAS Institute, Cary NC).

Two graphs were generated from the fitted model. The first graph shows observed and predicted HDRS-28 trajectories for each patient over time with model-based 95% confidence intervals. According to the model, a particular mode within a patient had the same slope for each episode. The second graph shows the observed and fitted values of HDRS-28 change within each contiguous episode using the same mode; the value at the last observation of a previous mode has been subtracted from each observation at the subsequent mode.

Stimulation location

The study protocol required the electrodes to be placed on the L-DLPFC. Imaging data for 4 subjects that were enrolled at the Medical College of Wisconsin were used to assess the effect of location on clinical outcomes. The pre-operative magnetic resonance imaging (MRI) and post-operative computed tomography (CT) scans were fused using Analyze version 10 (AnalyzeDirect, Lenexa, KS) to determine the site of implanted electrodes. The pial surface for each subject was then extracted from the pre-operative MRI via Freesurfer (Martinos Center for Biomedical Imaging). A stimulated region of interest (ROI), calculated and displayed using MATLAB (Mathworks Inc, Natick, MA) and SCIRun (Center for Integrative Biomedical Computing, University of Utah), was defined as a locus of points on the pial surface within a 1-cm radius of each electrode. The analysis for mapping the ROI did not take into account the difference between anodic and mixed stimulation. However, a quantitative comparison of the effects of stimulation polarity and location in between-subjects and within-subjects data is essential and will be addressed in future studies. Each patient ROI was then mapped to one patient brain, which served as an atlas brain, for comparison (Fig. 1). The ROI for each patient was saved as a matrix of node values. These nodes were then mapped to the atlas brain using a template-matching algorithm in Freesurfer. Lastly, the nodes were color coded in SCIRun based on maximum percent improvement observed in HDRS-28.

Results

Stimulation effectiveness varied as a function of mode and duration

Eleven patients were assessed over the course of 104 weeks. For the present analysis, all patients (active and sham) were normalized so that baseline (Week 0) was the point at which stimulation was turned on. Stimulation effectiveness as a function of duration and mode are shown in a piece-wise linear mixed model for each subject (Fig. 2). Clinical response was defined as a 40% reduction in the HDRS-28 score from baseline. Eight subjects (Patients 1–8) were responders under this criterion. The linear models for each mode were grouped to their respective categories (anodic full power, anodic reduced power, and mixed polarity) (Fig. 3). A statistically significant improvement in HDRS-28 was observed during the application of anodic full power modes (slope $= -0.109$, $P = 0.034$). A statistically significant effect was also observed during the application of the mixed polarity modes (slope $= -0.26$, $P < 0.001$). However, improvement during anodic reduced power modes did not reach significance ($P > 0.05$). Lastly, improvement during the initial 8-week period contributed greatly to the effect of anodic modes at full power (Fig. 4).

Response probability increased over time

A Kaplan–Meier curve was used to determine the time necessary to observe a clinical effect of the EpCS (Fig. 5). Analysis of the baseline HDRS-28 showed that it had no predictive effect on the time of response ($P = 0.63$). Over 50% of the responses (5 out of 8) occurred within the first 20 weeks of the study as shown in Fig. 2. In comparison, only three subjects displayed a clinical response at 8 weeks, which was the end-point in the clinical trial. These results were generated using a 40% improvement threshold. When the response probability was evaluated with a threshold of 50% improvement form baseline, the results were similar. By week 20, 50% of the responses (3 out of 6) had occurred.

Stimulation effectiveness was location-dependent

An average value for the maximum improvement from baseline HDRS-28 was calculated at each of the nodes that were mapped in

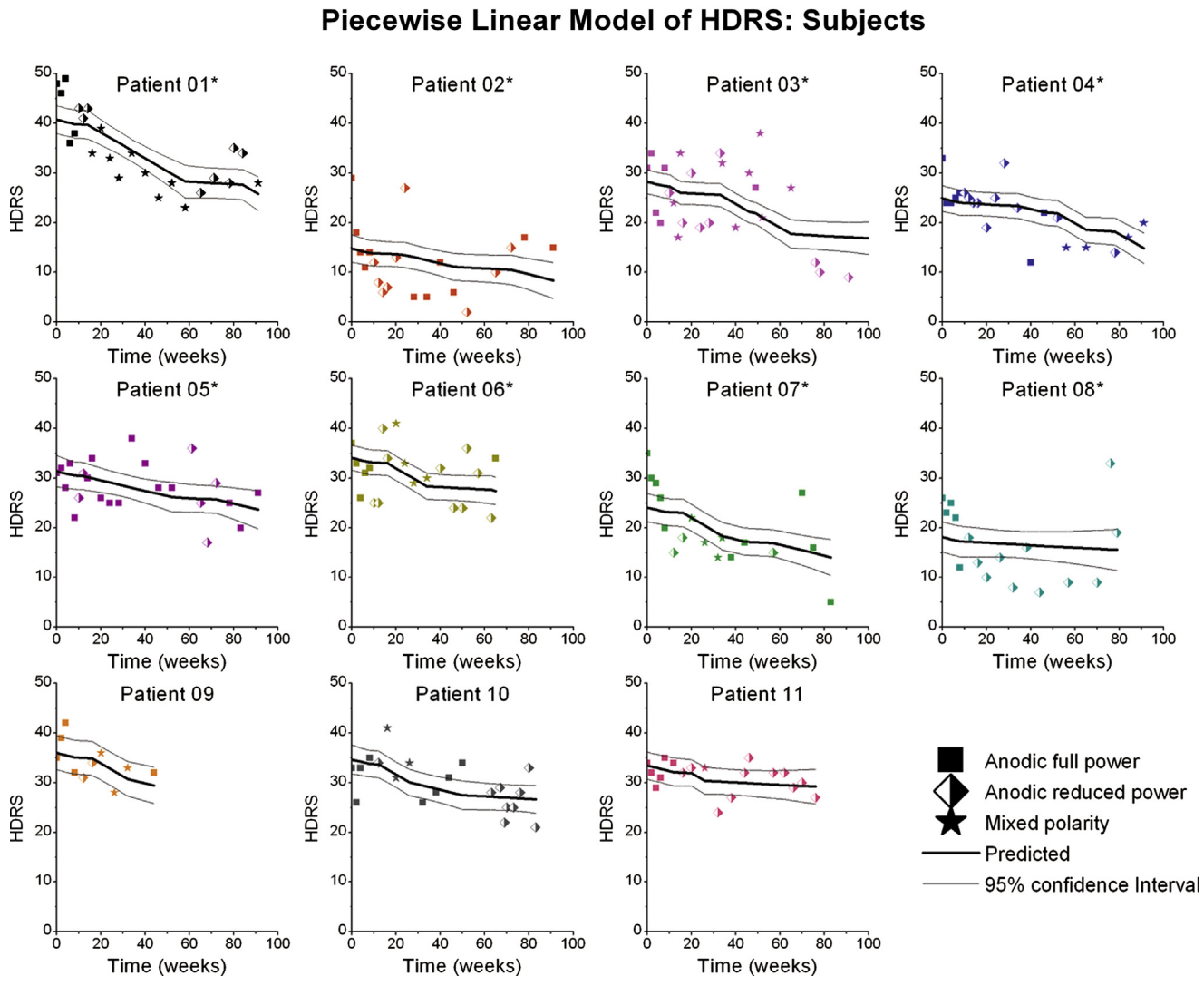

Figure 2. Piece-wise linear mixed model for each patient based on stimulation mode. Each contiguous episode of a stimulation mode within a patient was linearly modeled. Of the 11 subjects, 8 were clinical responders over the course of 104 weeks. *Patient reached criteria for clinical response during the 104 week study period.

the ROI. The improvement ranged from 52% to 93%. Nodes in the medial and posterior areas correlated with lower improvement values (red) while those in the lateral and anterior areas correlated with higher improvement values (blue). This suggests a trend that stimulation in the lateral and anterior region of the L-DLPFC correlates with better clinical outcomes (Fig. 6). This result illustrates a sub-region within the L-DLPFC that could serve as a target for future therapies.

Discussion

The goal of this study was to assess the degree of variability in HDRS-28 due to changes in stimulation protocol or electrode location. In particular, the aims of this study were to determine if changes in the stimulation protocol (anode/cathode) had a differential effect on HDRS-28, to estimate the time necessary for treatment to evoke a clinical response, and to explore the effects of stimulation location on clinical outcome.

Based on the effects of cathodal and anodal stimulation [17,18], we would expect the mixed polarity modes to have had a minimal effect. Contrary to this theory, the results indicated a significant effect of the mixed mode on the improvement of HDRS-28. One reason for this could be the magnitude of the current delivered. Current delivery was more focused in mixed mode because only one contact was active at a time during stimulation and therefore all of the current (6.5 mA) was delivered through that electrode. Also, anodes and cathodes are selective in which neural elements are excited. Because the mixed polarity modes allowed for each electrode to serve as an anode and a cathode, a wider range of neural elements may have been recruited. Lastly, the direction of the polarizing effect is influenced by the orientation of dendrites and axons in the induced electrical field [18]. The improvement due to mixed mode application could be attributed to the neuron orientation(s) underneath the cortical surface. This claim could be further investigated by exploring the effects of selective stimulation on the longitudinal outcomes of other neuromodulation techniques such as rTMS which allow for control of the electric field orientation relative to cortical tissue.

The results demonstrate that improvement was also significant with the anodic full power modes. The effect of the anodic full power modes was observed mostly in the initial period (8 weeks), and in some patients most of the improvement was

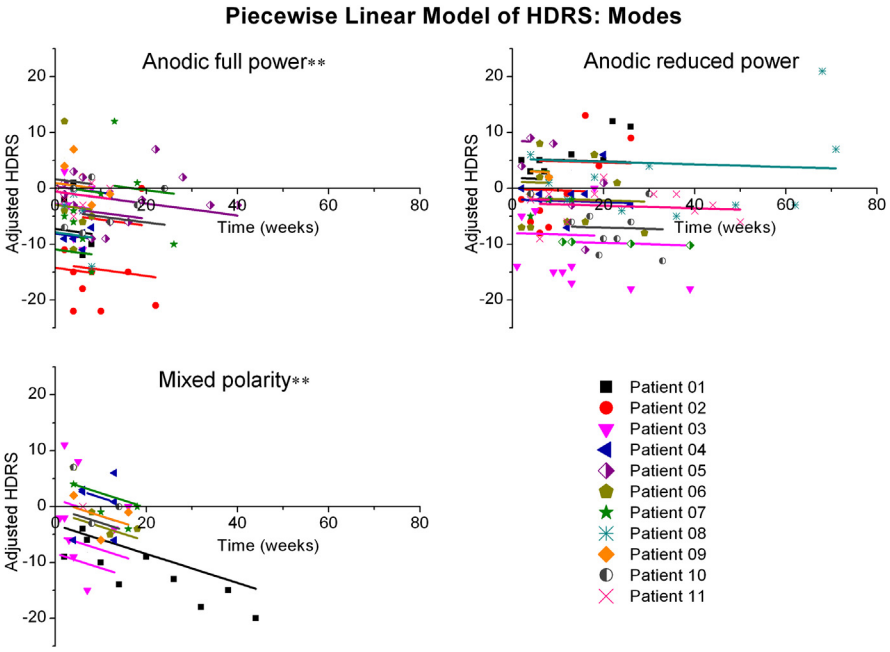

Figure 3. Piece-wise linear mixed model for each mode. The slopes obtained for each contiguous stimulation mode as displayed in Fig. 2 were grouped to study the effect of stimulation parameters. The improvement in HDRS-28 during the application of the anodic mode at full power was statistically significant (slope = −0.109, $P = 0.034$). Improvement in HDRS-28 during mixed mode was also statistically significant (slope = −0.26, $P < 0.001$). However, anodic modes at reduced power did not have an effect on HDRS-28 ($P > 0.05$). **Modes showed statistically significant improvement.

achieved during this period. Therefore, due to a floor-effect, other modes may have been unable to improve response further (Fig. 4). When looking closely at the data, the subjects can be divided into fast versus slow responders. The floor-effect could be observed in the fast responders. Ideally, a statistical comparison of anodic full power modes applied initially versus later in the study would provide more perspective. However, due to limited data points for the latter condition, this analysis was not possible. A similar trend was observed for HDRS improvement in a DBS study for MDD during the initial 2 months of treatment [4]. It is also essential to note the effects of duty-cycle on clinical outcome since discontinuous stimulation may have an impact on the long-term sustainability of treatment [6]. However, according to our results, the intermittent stimulation which was characterized by a lower duty cycle (anodic reduced power) was not effective.

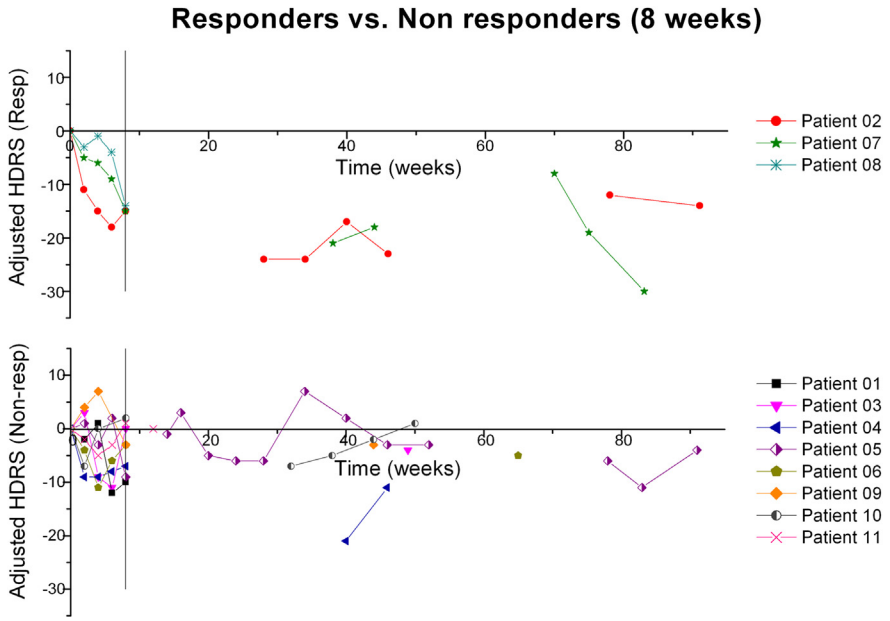

Figure 4. Responders versus non-responders at 8 weeks. The effect of anodic mode at full power at initial versus later time points in both responders and non-responders. The data shown are for responders (top panel, $n = 3$) and non-responders (bottom panel, $n = 8$) during the initial 8 weeks of stimulation. The vertical lines in each plot indicate the initial 8-week period. Responders improved dramatically in the initial period and may have experienced a floor-effect which limited further improvement.

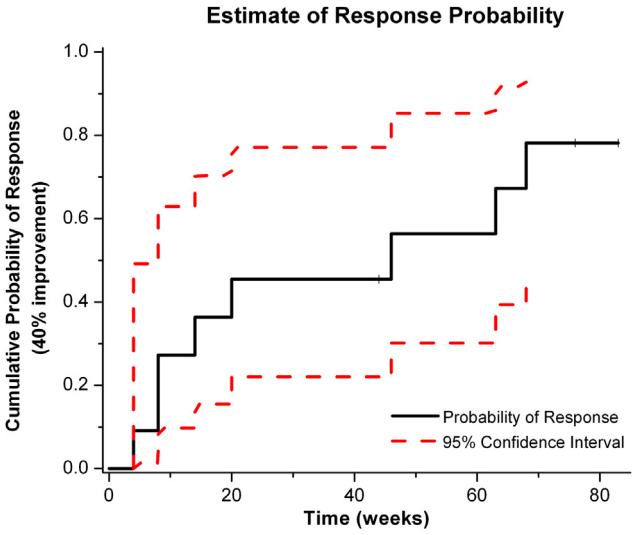

Figure 5. Kaplan–Meier estimate of response probability. Each step in the solid black line indicates that one or more patients reached the response criterion.

The time course for response to EpCS was variable, which could result from many possible factors including the characteristics of the patient, life events that occurred during the study period, stimulation location and stimulation protocol (including mode). There are periods of improvement in individual patients during which the stimulation protocol was fixed and the HDRS-28 scores declined steadily over a period of weeks. Hence, the data suggests that therapeutic response is due to some type of plasticity brought about by chronic stimulation. Cortical excitability is modulated by altering resting potential during stimulation and by modifying synaptic transmission [12,21]. Also, the neuro-chemical and neuro-endocrine processes that are responsible for expression of secondary messengers are time consuming and complicate the programming algorithms necessary to observe efficacy in EpCS [18]. When considering the results of different stimulation modes it is important to note the possibility of metaplasticity. Metaplasticity is a term used to describe the changes that occur in plasticity due to neuronal influences from previous treatments steps and medications. This can influence subsequent changes in plasticity and affect both response and relapse.

It is widely accepted that MDD is heterogeneous [2] and therefore, patient response rates will inherently vary. A recent pharmacological study, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial [22], concluded that remission rates decrease with an increase in the number of acute treatment steps. Despite the longer amount of time taken by some of the subjects to reach remission, the study noted that remission was associated with better prognosis even when achieved after numerous treatment steps. Thirty five percent of patients with MDD required more than eight weeks to reach remission with their first antidepressant. This further emphasizes that physiological change necessary to cause and sustain improvement occurs at different rates in different individuals. The results of our response probability analysis suggest that in order to observe a clinical response in over half the responders, the treatment outcome should be evaluated at 20 weeks instead of 8 weeks. In another recent EpCS study [6], average improvement in HDRS-24 was only 36% from baseline at 16 weeks whereas at 28 weeks the average improvement was 55% from baseline. These findings further support our results.

The role of L-DLPFC in neuropsychological disorders has been investigated before. In MDD, the DLPFC tends to be hypometabolic while the ventro-medial prefrontal cortex (VMPFC), including subgenual cingulate (Cg25) is hypermetabolic. There is also evidence of high connectivity between the prefrontal cortex and the limbic structures. To evaluate the effects of location on stimulation, a transcranial direct current stimulation (tDCS) study [12] compared stimulation at the prefrontal cortex with an active control group which was stimulated at the occipital cortex. At the end of their study, there were a significantly greater number of responders in the active treatment group than in either the sham or the active control group [12]. However, choosing L-DLPFC as a target for stimulation is still ambiguous due to the broad area that it covers. It is unclear where electrodes should be placed during EpCS in order to maximize efficacy of the treatment. The last analysis in this study was aimed at exploring the effects of stimulation location on clinical outcome. Our data suggests a trend in which stimulating in the anterior and lateral regions of the L-DLPFC is more efficacious than posterior and medial regions. This finding is significant as it emphasizes the importance of stimulation location. With an anterior and lateral placement of the electrode, the stimulation is more likely to be in an effective region of the DLPFC. In a rTMS study for depression [15], 54 patients were stimulated over the prefrontal cortex for 3 weeks. They found that there was a linear relationship between coil placement and HDRS improvement. According to their results, there was a 5 mm difference in the average coordinate position of the non-responders and the responders in all three axes (x, y, z). They were unable to observe the same dependence on the coil position in the placebo group. Likewise, they also concluded that stimulating lateral and anterior in the DLPFC was associated with better clinical response.

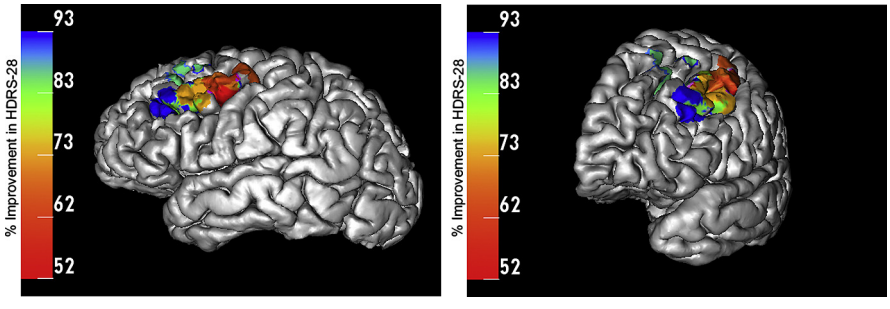

Figure 6. Stimulation in the lateral and anterior region of the L-DLPFC correlates with better clinical outcome. An average value for the maximum improvement from baseline HDRS-28 was calculated at each of the nodes that were mapped in the ROI. Improvement ranged from 52% to 93%. Nodes in the medial and posterior areas were correlated with lower improvement values (red) while those in the lateral and anterior areas were correlated with higher improvement values (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Conclusions

A persistent problem in neuromodulation trials has been the difficulty in quantifying outcome variability. In general, clinical trials are designed to tightly control treatment such that outcome variability is attributed to differences among patients in the study cohort. However, neuromodulation therapies such as EpCS have many additional sources of variability including electrode location and stimulation protocol. The methods used in this study confirm that quantitative comparison of stimulation among different patients can be accomplished by a pipeline of analysis tools. While the results of our study contribute largely to the understanding of EpCS, we believe that this approach can provide insights to many types of neuromodulation studies by first quantifying where and how individual patients were stimulated, and secondly by correlating stimulation location with effectiveness. Importantly, we believe that this approach can provide insights whether or not a study reached its therapeutic objectives.

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