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Effects of Subcallosal Cingulate Deep Brain Stimulation on Negative Self-bias in Patients With Treatment-resistant Depression

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ABSTRACT

Background: The cognitive neuropsychological model states that antidepressant treatment alters emotional biases early in treatment, and after this initial change in emotional processing, environmental and social interactions allow for long-term/sustained changes in mood and behavior.
Objective: Changes in negative self-bias after chronic subcallosal cingulate (SCC) deep brain stimulation (DBS) were investigated with the hypothesis that treatment would lead to changes in emotional biases followed by changes in symptom severity.
Methods: Patients ($N = 7$) with treatment-resistant depression were assessed at three time points: pre-treatment; after one month stimulation; and after six months stimulation. The P1, P2, P3, and LPP (late positive potential) components of the event-related potential elicited by positive and negative trait adjectives were recorded in both a self-referential task and a general emotion recognition task.
Results: Results indicate that DBS reduced automatic attentional bias toward negative words early in treatment, as indexed by the P1 component, and controlled processing of negative words later in treatment, as indexed by the P3 component. Reduction in negative words endorsed as self-descriptive after six months DBS was associated with reduced depression severity after six months DBS. Change in emotional processing may be restricted to the self-referential task.
Conclusions: Together, these results suggest that the cognitive neuropsychological model, developed to explain the time-course of monoamine antidepressant treatment, may also be used as a framework to interpret the antidepressant effects of SCC DBS.

Introduction

According to cognitive models, negative self-bias is a defining characteristic of depression [1–5]. Negative self-bias refers to an emotion-by-depression interaction; depressed individuals may have increased negative emotional processing [6], reduced positive emotional processing [7], or a combination of the two. The relationship between negative self-bias and the mood disturbances characteristic of depression has recently attracted considerable interest.

Effective antidepressant treatment alters emotional processing biases, often in advance of detectable improvement in other depression symptoms. The cognitive neuropsychological model of depression holds that monoamine antidepressant treatment causes early alterations of emotional biases independently from changes in mood [8–11]. After the initial change in emotional processing, environmental and social interactions allow for changes in mood and behavior following, and dependent on, change in emotional biases [9]. According to the model, this explains why monoamine antidepressant treatment may take weeks or months before clinically significant reduction in symptoms occurs.

Changes in negative emotional bias with antidepressant treatment could be due to a reduction in processing negative stimuli or an enhancement in processing positive stimuli. For example, administration of the selective serotonin reuptake inhibitor citalopram for one week reduced the identification of

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fearful, angry, and disgusted facial expressions [12]. By contrast, administration of a single dose of the norepinephrine reuptake inhibitor reboxetine increased recognition of happy facial expressions [13]. Thus, a full accounting of the influence of antidepressant treatment on emotional biases requires an exploration of processing of both negative and positive stimuli.

Self-bias can be quantified using an emotional self-referential task in which participants are asked to indicate whether adjectives describing positive and negative personality traits are self-descriptive [14–16]. Emotional self-referential processing involves activation within a network of brain areas including medial prefrontal cortex (MPFC) and subcallosal cingulate (SCC) [17–21]. Yoshimura and colleagues [22] found that depressed participants had hyperactivity in MPFC and SCC when processing negative words in a self-referential task compared to non-depressed controls. Further, Yoshimura and colleagues [23] found that twelve weeks of cognitive behavioral therapy reduced functional activation of the MPFC and SCC in response to negative words, and increased activation for positive words. Lemogne and colleagues [24] suggested that hyperactivity in the ventral MPFC reflects increased automatic attention to self-referential information in depression, and hyperactivity in the dorsal MPFC reflects strategic control processes such as the comparison of self-referential information to negative internal models of the self in depression. Thus, antidepressant treatment may modulate both automatic and controlled processes; and may both reduce processing of negative self-referential information, and enhance processing of positive self-referential information.

The cognitive neuropsychological model suggests that changes in emotional bias early in monoamine antidepressant treatment are due to alterations in bottom-up, automatic processing biases rather than strategic control processes. In contrast, cognitive therapy directly targets top-down, strategic control processes [9,25]. The temporal resolution of event-related potentials (ERPs) allows an examination of whether antidepressant treatment affects automatic processes and/or strategic control processes. In an emotional self-referential task, Shestyuk and Deldin [26] found that non-depressed controls had greater P2 amplitude for positive words, whereas currently depressed and remitted depressed had greater P2 amplitude for negative words. In addition, they found that non-depressed and remitted depressed groups had greater late positive potential (LPP) amplitude for positive words, whereas the currently depressed group had greater amplitude for negative words. These results suggest that both currently and remitted depressed patients have automatic attentional biases toward negative self-referential information as revealed by the P2, but only currently depressed patients show a bias toward negative self-referential information during controlled processing as revealed by the LPP. Thus, effective antidepressant treatment evidently altered controlled but not automatic processing biases.

In the current study, longitudinal changes in emotional self-referential processing associated with chronic SCC deep brain stimulation (DBS) were investigated in patients with treatment-resistant depression (TRD). Sustained antidepressant effects have been demonstrated with chronic SCC DBS in patients with TRD [27–30]. Previous studies of SCC DBS have identified cerebral blood flow and glucose metabolic changes with antidepressant response to DBS, including changes in MPFC and dorsal lateral PFC, as well as SCC and dorsal anterior cingulate [29,30]. Changes with DBS overlap areas of regional change also seen with antidepressant response to other treatments including medications and cognitive behavioral therapy [25,28,31]. These studies suggest that depression and alterations in self-bias are associated with abnormal activity in a network of areas including MFC and SCC, and that DBS of the SCC can normalize the activity in these brain regions. Therefore, it seems likely that DBS of the SCC may alter emotional self-referential processing.

To examine changes in negative self-bias after DBS treatment, TRD patients were assessed at three time points (pre-treatment, after one month stimulation, and after six months stimulation) to examine both early and late effects of DBS treatment. The P1, P2, P3, and LPP components of the event-related potential (ERP) elicited by positive and negative trait adjectives were recorded in both a self-referential task and a general emotion recognition task. In the self-referential task, participants indicated whether the words were self-descriptive. In the general emotion recognition task, participants indicated whether the words described a socially desirable trait. The ERP components analyzed reflect dissociable aspects of emotional stimulus processing. Modulation of the P1 reflects attention to emotional words [32]. The P2 component reflects automatic monitoring of semantic meaning [26]. In this context, modulation of the P3 has been shown to correspond to the motivational relevance of emotional stimuli [33], and likely reflects controlled processing of the stimuli. The early and late LPP also reflect controlled cognitive processing of the emotional words [26], but the early LPP (<600 ms) may also be sensitive to changes in the stimulus [37]. Thus, this series of ERP components captures the temporal dynamics of emotional self-referential processing, and allows assessment of both bottom-up, automatic processes and top-down, strategic control processes.

This study investigated whether predictions from the cognitive neuropsychological model, developed to explain monoamine antidepressant effects, might also hold for SCC DBS antidepressant treatment. Specifically, five questions were addressed: (1) Does SCC DBS alter processing of positive and/or negative self-referential information? (2) Do changes in negative self-bias occur early (after one month SCC DBS) and/or later (after six months SCC DBS) in treatment? (3) Does SCC DBS alter automatic and/or strategic processes? (4) Are changes in negative self-bias after SCC DBS associated with changes in other depression symptomology as assessed by the Hamilton Depression Rating Scale [34]? (5) Are any changes in emotional bias related to SCC DBS restricted to the self-referential task or do they also occur in the general emotion recognition task?

Methods

Participants and SCC DBS intervention

Seven patients with TRD participating in a clinical research trial of DBS for depression (three men/four women, five unipolar/two bipolar, mean age = 39.6 years, SD = 10.2 years) were included in this study. Inclusion and exclusion criteria for this study have been previously described [27]. Patients remained on stable medications for four weeks prior to surgery and through the first six months of chronic DBS treatment. The 17-item HDRS was rated weekly at clinical follow-up visits and used as the primary outcome measure of treatment efficacy in the clinical trial [27] and for correlative analyses (see below). All patients gave written informed consent and the study was approved by the Institutional Review Boards of Emory University and Georgia Institute of Technology.

Behavioral and neurophysiological paradigm

Behavioral testing and electrophysiological recording occurred at three time points during the DBS study: at baseline prior to implantation of DBS electrodes; after one month of active SCC DBS; and after six months of active SCC DBS. Stimulation was turned off during the experiment to avoid EEG artifacts due to the stimulator. As previously reported, following initiation of chronic

stimulation, SCC DBS is not associated with acute perceived or observed changes in behavior with acute on versus off stimulation [27,35].

During the emotional self-referential task, participants were presented with a set of 80 adjectives that pertain to personality traits. Of these, 40 were positive words (e.g., sincere, careful, warm) and 40 were negative words (e.g., unlikeable, moody, tense). All 80 words were presented within one continuous block, with order of word presentation randomized during each testing session. For each trial, a fixation cross appeared at the center of the screen for 1 s, which was then replaced by a word that remained on screen until the participant responded. Participants indicated whether the word was self-descriptive by pressing one of two keys on a standard keyboard ('1' for yes; '2' for no). After each response, a new trial began with the presentation of the fixation cross. The proportion of 'yes' responses and the response time to make the decision were recorded for the positive and negative words.

After the self-referential task, participants performed a general emotion recognition task. The general emotion recognition task was identical to the self-referential task except that participants indicated whether the words described a socially desirable trait.

Electrophysiological recording and offline data preparation

Electrophysiological data were recorded using the Active-Two amplifier system (BioSemi, Amsterdam, Netherlands) and data were digitized at 512 Hz. Electrode locations included: FP1/2, F7/8, F3/4, Fz, C3/4, Cz, P7/8, P3/4, Pz, T7/8, O1/2, Oz, AF3/4, FC1/2, CP1/2, PO3/4, FC5/6, and CP5/6. The BioSemi system requires the placement of two additional electrodes, the common mode sense (CMS) and driven right leg (DRL).

EEG data were processed using BrainVision Analyzer (Brain Products, Gilching, Germany). Vertical electrooculogram (EOG) was calculated offline as the difference between electrodes positioned above and below the left eye. Horizontal EOG was calculated offline as the difference between electrodes positioned on the outer canthi of the left and right eyes. Offline, scalp channels were re-referenced to the average of all channels. Digital filtering was performed offline using a band-pass .1–30 Hz zero phase shift Butterworth filter (12 dB/oct).

Continuous EEG was segmented into 1700 ms epochs starting 200 ms before the presentation of the emotional words. Ocular artifacts were corrected using standard regressive methods [36]. The segments were baseline corrected relative to the 200 ms baseline. Artifact correction was conducted by rejecting segments if the voltage step exceeded 50 μV/ms, the difference between maximum and minimum voltage exceeded 300 μV, or there was low activity below .5 μV. The trials were then averaged separately for each condition for each participant.

P1 (150–170 ms), P2 (255–275 ms), and P3 (310–360 ms) amplitudes were quantified as the mean activity in the indicated time windows. These time windows were chosen based on the peaks in the grand average waveform across all participants and conditions. "Early" late positive potential (LPP; 400–600 ms) and "late" LPP (600–800 ms) amplitude were quantified as the average activity in the indicated time windows, and these windows were chosen based on prior studies [26,37]. We used the two separate LPP intervals because early and late LPP may reflect distinct processes [37]. Voltage was averaged across electrodes P3, Pz, and P4 to obtain the dependent measure as preliminary analyses did not show any hemispheric differences. These electrode sites were chosen because the components of interest (P1, P2, P3, LPP) were maximal at these sites.

Statistical analysis

To assess changes in behavior and electrophysiology after DBS, non-parametric Wilcoxon Signed Ranks tests were used due to small sample size. For each dependent measure, we assessed whether there was a change for negative words or positive words after one month or six months DBS relative to baseline.

To assess relationships between change in emotional bias and change in depression symptomology, percent change measures were calculated for behavioral and electrophysiological responses to negative words and positive words after one month and six month DBS relative to baseline. Percent change was also calculated for depression severity as measured by HDRS after one month and six month DBS relative to baseline. Correlations between each of these percent change measures were examined using Spearman's rho.

Results

Self-referential task

Behavioral results

Overall, the results indicate a reduction in negative words endorsed as self-descriptive after one month and six months DBS (see Fig. 1). After one month DBS, there was a statistically significant decrease in the proportion of negative words endorsed as self-descriptive ($M = .49$, $SD = .27$) compared to baseline ($M = .72$, $SD = .09$), $z = 2.20$, $P = .028$. The change in proportion of positive words endorsed was not statistically significant after one month

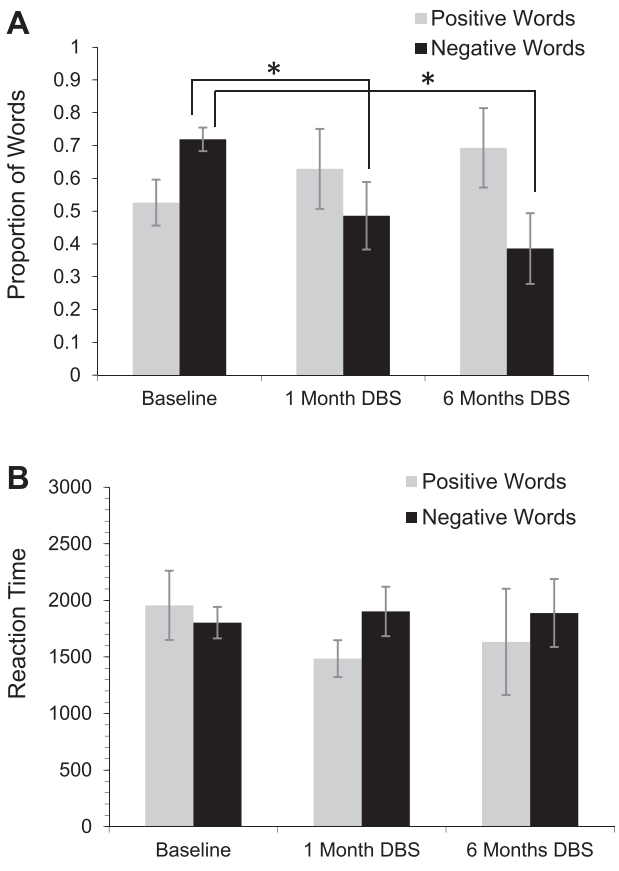

Figure 1. Behavioral results from the self-referential task as a function of word valence (positive vs. negative) and time point (baseline vs. one month DBS vs. six months DBS). (A) The proportion of words endorsed as self-descriptive. (B) Reaction time to endorse words as self-descriptive. *denotes statistically significant changes relative to baseline at $\alpha = .05$.

DBS ($M = .63$, SD = .32) compared to baseline ($M = .53$, SD = .19), $z = 1.36$, $P = .176$. After six months DBS, there was a statistically significant decrease in the proportion of negative words endorsed as self-descriptive ($M = .39$, SD = .29) compared to baseline, $z = 2.37$, $P = .018$, but the increase in the proportion of positive words endorsed as self-descriptive ($M = .69$, SD = .32) compared to baseline, $z = 1.69$, $P = .091$, was not statistically significant. There were no statistically significant effects of DBS on response times ($zs < 1.01$, $Ps > .310$).

Electrophysiological results

The results indicate a reduction in P1 amplitude for negative words after one month DBS, and a reduction in P1 and P3 amplitude for negative words after six months DBS (Fig. 2), relative to baseline.

P1 component. After one month DBS, there was a significant reduction in P1 amplitude for negative words, $z = 2.37$, $P = .018$, but there was not a significant change in P1 amplitude for positive words, $z = .51$, $P = .612$. After six months DBS, there was a significant reduction in P1 amplitude for negative words, $z = 2.20$, $P = .028$, but there was not a significant change in P1 amplitude for positive words, $z = .00$, $P = 1.0$.

P2 component. There were no significant changes in P2 amplitude with either one month or six months DBS ($zs < .68$, $Ps > .499$).

P3 component. For negative words, the decrease in P3 amplitude after one month DBS, $z = 1.69$, $P = .091$, was not statistically significant, but there was a statistically significant decrease after six months DBS, $z = 2.37$, $P = .018$. There were no statistically significant changes in P3 amplitude for positive words ($zs < .85$, $Ps > .398$).

Early LPP (400–600 ms). There were no statistically significant changes in early LPP amplitude ($zs < 1.86$, $Ps > .063$).

Late LPP (600–800 ms). There were no statistically significant changes in late LPP amplitude ($zs < 1.18$, $Ps > .237$).

Correlations

The correlation between the percent change in negative words endorsed as self-descriptive after one month DBS ($M = 32.4\%$, SD = 34.4%) and percent change in depression severity after one month DBS ($M = 26.4\%$, SD = 15.2%) was not statistically significant, $rs = .36$, $P = .432$. In contrast, percent change in negative words endorsed as self-descriptive after six months DBS ($M = 45.5\%$, SD = 38.5%) was strongly correlated with percent change in depression after six months DBS ($M = 54.9\%$, SD = 25.7%), $rs = .96$, $P = .0005$ (Fig. 3). No other correlations were statistically significant.

General emotion recognition task

Analyses replicating those for the self-referential task were conducted, but no statistically significant differences in the behavioral or ERP measures (Fig. 2, right panels) were found after one month or six months DBS.

Discussion

As hypothesized and predicted by the cognitive neuropsychological model, patients with TRD undergoing SCC DBS experienced behavioral and physiological changes in emotional self-bias, which was associated with subsequent clinical improvement. Specifically, after one month of chronic DBS, TRD patients had a reduction in negative self-bias which was most evident in the reduction of negative words endorsed as self-descriptive, and reduction in P1 amplitude elicited by negative words relative to baseline. After six months DBS, TRD patients maintained the reduction in negative self-bias which again was most evident in the reduction of negative words endorsed as self-descriptive, and in reduction of P1 and P3 amplitude elicited by negative words relative to baseline. In addition, percent change in proportion of negative words endorsed as self-descriptive was highly correlated with the percent change in depression severity after six months (but not one month) DBS. There were no statistically significant changes in behavioral or

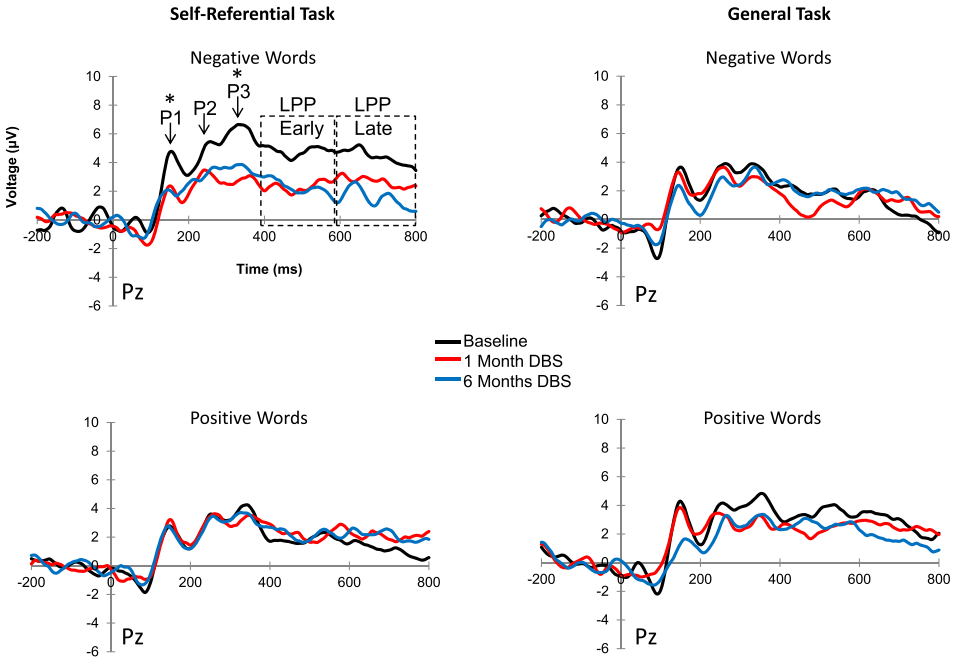

Figure 2. Event-related potentials elicited by positive and negative words at the three time points (baseline – black lines, one month DBS – red lines, and six months DBS – blue lines) in the self-referential task and general emotion recognition task at electrode Pz. *denotes statistically significant changes in ERP component amplitude relative to baseline at $\alpha = .05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

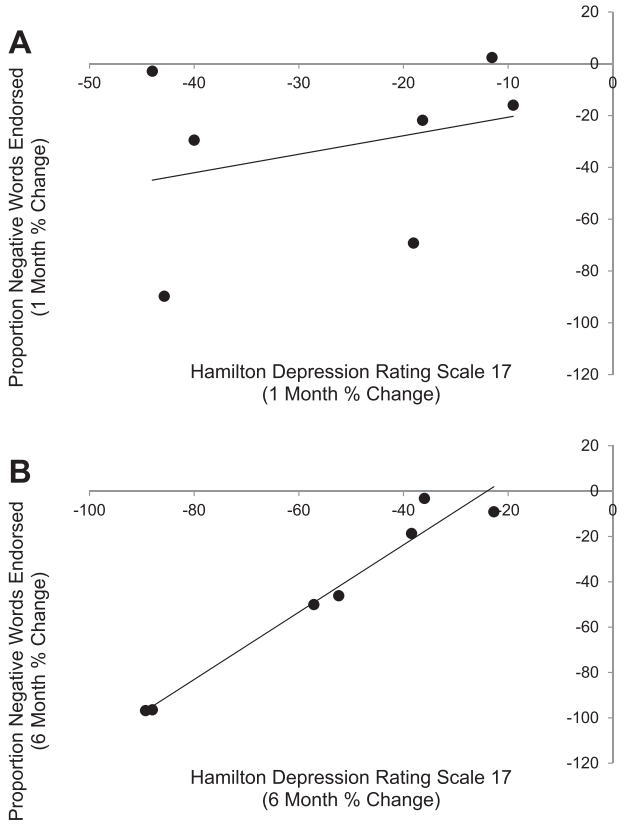

Figure 3. Relationship between percent change in proportion of negative words endorsed as self-descriptive and percent change in depression severity. (A) After one month DBS, the relationship between change in negative self-bias and depression severity was not statistically significant. (B) After six months DBS, there was a strong positive correlation between reduction in negative self-bias and reduced depression severity.

electrophysiology in the general emotion recognition task, suggesting that changes in emotional processing may be specific to the self-referential task.

The results suggest that SCC DBS alters negative self-bias early in treatment (i.e., after one month of active stimulation) by reducing automatic processing biases toward negative self-referential information as indexed by the P1 component. At baseline, the P1 component elicited by negative words in the TRD patients likely reflects an automatic attentional bias toward negative self-referential information [26,32]. Kissler and Herbert [38] have suggested that emotional processing can occur prior to cognitive processing because emotional processing needs fewer inferences. In other words, negative words captured the attention of the TRD patients even though semantic information about the word may not have been fully processed. This attentional capture may be a neural mechanism that contributes to the excessive focus on negative self-referential information exhibited in depression [26]. The reduction of P1 amplitude for negative words after one month of DBS suggests that DBS can attenuate this automatic attentional bias to negative emotional information relatively early in the time-course of treatment. This early effect is consistent with the self-reported shift in negative interoceptive sensations with acute stimulation in the operating room observed in the majority of patient [27,30].

Later in treatment (after six months of active stimulation), the results indicate that SCC DBS alters negative self-bias by reducing strategic, controlled processing of negative self-referential information as indexed by the P3 component. The P3 component is thought to reflect controlled processing and has been shown to correspond to the motivational relevance of emotional stimuli [33]. The greater P3 amplitude for negative words at baseline then likely reflects controlled, sustained attention and elaboration of negative self-referential information. Reduction in P3 amplitude after six months DBS may reflect decreased rumination over negative self-referential information.

Shestyuk and Deldin [26] proposed a model of negative self-bias that states that persistent rumination over negative self-referential information helps establish automatic attention biases towards this type of information. In turn, these automatic attentional biases continually provide negative self-referential information to ruminate over. Effective antidepressant treatment can break this cycle by reducing rumination over negative self-referential information. Furthermore, Yoshimura and colleagues [23] recently demonstrated that cognitive behavioral therapy, which directly targets negative self-biases, results in reduced functional activation of the MPFC and SCC. The P3 component measured here may also reflect changes in the MPFC and SCC due to DBS as these are the same brain areas that show functional changes with SCC DBS treatment [29,30]. Thus, as DBS alters activity in the MPFC and SCC, this may in turn change negative self-bias by reducing sustained attention and elaboration to negative self-referential information as indexed by changes in the P3 component.

Rather than a generalized effect of DBS, the anatomical specificity of the SCC target may have bearing on these findings. The SCC fibers impacted in this study include bundles to the MPFC, dorsal anterior cingulate, nucleus accumbens/thalamus, and brain stem [39,40]. Detailed tract tracing analyses demonstrate a more specific pathway from SCC to the dorsal raphe and periaqueductal grey [41,42]. This anatomical specificity has been directly linked to top-down control mechanisms in rodent models of depression [43–45], providing a putative mechanism for the differential impact of SCC DBS on negative but not positive emotional processing.

Taken together, these results suggest that the cognitive neuropsychological model can be applied to explain SCC DBS as well as monoamine antidepressant treatment. Early in treatment, SCC DBS reduces bottom-up, automatic processing of negative self-referential information. Later in treatment, once negative self-referential information no longer captures attention, DBS is able to influence top-down, cognitive control mechanisms. According to the model, the TRD patients were thus helped to engage in environmental and social interactions with reduced negative self-bias, and this ultimately results in improved mood and behavior [9]. In support of this idea, six months of treatment coincides with the time-course of observed antidepressant effects in these TRD patients [27]. Moreover, the change in negative words endorsed as self-descriptive was highly correlated with the change in depression severity after six months DBS relative to baseline. Thus, full clinical response might only occur when controlled processes begin to normalize so that patients no longer ruminate over negative self-referential information. Such a process, seen here in longitudinal changes in both behavior and ERPs elicited in the self-referential task, might signal renewed capacity for cognitive and behavioral retraining or other adjunctive rehabilitative strategies to maximize patient functional recovery.

Limitations

Limitations of the current study should be considered. The same words were presented at the three time points for both the self-task and general emotion task, although they were presented in random order during each testing session. Thus, it is possible that change in performance and ERP amplitude in the self-task was due to previous exposure. However, given that the change was different for positive and negative words, this explanation is less likely. Another limitation

was that the self-task was always performed before the general emotion task. Thus, the lack of change in the general task could be due to habituation. This limits our ability to make a strong conclusion regarding the specificity of the effects of DBS on self-referential emotional processing. However, note that the cognitive neuropsychological model of depression argues that treatment causes early alterations of emotional biases (not self-referential emotional processing per se) independently from changes in mood. After the initial change in emotional processing, environmental and social interactions allow for changes in mood and behavior following, and dependent on, change in emotional biases. An additional limitation was that the sample size was small and multiple-comparison corrections were not performed. This is a unique sample and first observation, and additional studies with larger samples will be necessary to confirm the results. Although SCC DBS is not associated with acute perceived or observed changes in behavior with acute on versus off stimulation [27,35], it is possible that the results reflect an effect of acute cessation of stimulation because the stimulator was turned off prior to each experimental session. In addition, there was no testing during sham DBS. Furthermore, medications differed across patients (e.g., some patients were taking benzodiazepines). However, there were no changes in medication over the course of the study with medication doses stable for at least four weeks prior to DBS surgery and for the duration of the study period described here. Because these data report mainly on changes over time within the study, the effect of concurrent medications should be minimized because doses were held steady. Future studies should employ a larger sample, finer time sampling, evaluate other TRD patient groups with different treatments, and examine possible interactions between medication and DBS.

Conclusions

Effects of SCC DBS on negative self-bias in patients with TRD were investigated. The results demonstrated that: (1) SCC DBS altered processing of negative self-referential information; (2) changes in negative self-bias occurred both early (after one month SCC DBS) and later (after six months SCC DBS) in treatment; (3) SCC DBS altered automatic processes early in treatment and controlled processes later in treatment; (4) reduction in negative words endorsed as self-descriptive was associated with a reduction in depression severity after six months DBS; (5) and changes in emotional bias may be restricted to the self-referential task. Together, these results suggest that the cognitive neuropsychological model, developed to explain the time-course of monoamine antidepressant treatment, may also be used as a framework to interpret the effects of SCC DBS.

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