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DORSOLATERAL PREFRONTAL CORTEX STIMULATION MODULATES ELECTROCORTICAL MEASURES OF VISUAL ATTENTION: EVIDENCE FROM DIRECT BILATERAL EPIDURAL CORTICAL STIMULATION IN TREATMENT-RESISTANT MOOD DISORDER

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Abstract—Electrocortical activity is increasingly being used to study emotion regulation and the impact of cognitive control on neural response to visual stimuli. In the current study, we used direct epidural cortical stimulation (EpCS) to examine regional specificity of PFC stimulation on the parietally-maximal late positive potential (LPP), an event-related potential (ERP) biomarker of visual attention to salient stimuli. Five patients with treatment-resistant mood disorders were stereotactically implanted with stimulating paddles over frontopolar (FP) and dorsolateral (DL) prefrontal cortex bilaterally. On their first day of activation, patients underwent sham-controlled EpCS coupled with 64-channel electroencephalograph (EEG) recordings and passive viewing of aversive and neutral images. In addition to sham, patients had either FP or DL prefrontal cortex stimulated at 2 or 4 V while they viewed neutral and aversive pictures. As expected during the sham condition, LPP was larger for aversive compared to neutral stimuli ($F(1,4)=232.07$, $P<.001$). Stimulation of DL compared to FP prefrontal cortex resulted in a reduction of the LPP ($F(1,4)=8.15$, $P=.048$). These data provide additional and unique support to the role of the DL prefrontal cortex in regulating measures of neural activity that have been linked to emotional arousal and attention. Future studies with EpCS can help directly map out various prefrontal functions in treatment-resistant mood disorder.

Key words: brain stimulation, attention, IAPS, late positive potential.

Emotion regulation describes the ability to modulate the intensity and quality of responses to emotional stimuli (Gross and Thompson, 2007). Successful emotion regulation has been linked to well-being, whereas difficulties regulating emotion appear to characterize various forms of psychopathology, including major depressive disorder- (Gross and John, 2003). Indeed, a hallmark clinical feature of major depressive disorder is the inability to disengage from negative memories, feelings and thoughts (Nolen-Hoeksema, 2000). Some have proposed that in depression the prefrontal cortex loses its ability to govern and modulate deeper limbic regions associated with primary emotional drive (George et al., 1994; Johnstone et al., 2007). Cognitive behavioral therapy may be seen as an attempt to restore cortical control over emotional input and processing (Alexander et al., 1986).

Recent neuroimaging work has begun to explicate the neural correlates of successful emotion regulation. Many studies have now reported that the use of emotion regulation strategies results in diminished activity in emotion-related regions such as the amygdala, as well as increased activity in prefrontal regions of the brain implicated in cognitive control (Beauregard et al., 2001; Ochsner et al., 2002; Levesque et al., 2003; Kalisch et al., 2005; Phan et al., 2005; Harenski and Hamann, 2006; Ohira et al., 2006). For example, Phan and colleagues (2005) found that when participants decreased their emotional experience to unpleasant pictures using a cognitive control strategy, self-reported intensity of negative affect in response to the pictures was reduced, and increased activity in dorsal and lateral PFC was observed; moreover, bilateral DLPFC activation was inversely related to self-reported negative affect.

In addition to hemodynamic measures of neural activity, event-related brain potentials (ERPs) can be used to index the automatic and controlled processing of emotional stimuli (Schupp et al., 2004a; Keil et al., 2005; Foti and Hajcak, 2008; Hajcak et al., 2009). In particular, a parietally-maximal ERP referred to as the late positive potential (LPP) is larger following the presentation of arousing compared to emotionally neutral stimuli; the LPP is a relative positivity that begins within 200 ms following the onset of emotional stimuli, becomes maximal by 400 ms, and continues for the duration of stimulus presentation

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Abbreviations: DL, dorsolateral; ECT, electroconvulsive therapy; EEG, electroencephalography; EpCS, epidural cortical stimulation; ERP, event-related potential; fMRI, functional magnetic resonance imaging; FP, frontopolar; LPP, late positive potential; TMS, transcranial magnetic stimulation; TRMD, treatment-resistant mood disorders; V, volts; VNS, vagal nerve stimulation.

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(Cacioppo et al., 1994; Lang et al., 1997; Cuthbert et al., 2000; Schupp et al., 2000, 2003; Keil et al., 2002). The increased LPP for emotional compared to neutral pictures has been shown to be larger for those stimuli that are rated as more arousing and prompt the largest skin conductance changes (Cuthbert et al., 2000; Schupp et al., 2004b). Importantly, the impact of emotional content on the LPP have been shown to be independent of stimulus size (De Cesarei and Codispoti, 2006) and low-level perceptual characteristics of the stimuli (Bradley et al., 2007).

Consistent with the notion that emotional stimuli receive increased perceptual processing and attentional resources, studies that use both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) report that emotional stimuli activate visual and extrastriate cortex to a greater degree than neutral stimuli (Breiter et al., 1996; Lane et al., 1997; Bradley et al., 2003; Sabatinelli et al., 2004). A recent study in healthy adults combined ERP and fMRI methods found that the increased LPP elicited by emotional stimuli corresponded to increased blood flow in occipital, parietal, and inferotemporal regions in the brain—consistent with the parietal maximum of the LPP (Sabatinelli et al., 2004). The emotional modulation of the LPP appears to reflect increased visual attention to salient stimuli, which might depend on reentrant processes from amygdala to visual cortex (Lang et al., 1998; Morris et al., 1998; Bradley et al., 2003; Sabatinelli et al., 2005).

In a series of studies we have examined whether the amplitude of the LPP, like amygdala activity measured via fMRI, is sensitive to emotion regulation instructions. In an initial study, the LPP was reduced following reappraisal instructions (Hajcak and Nieuwenhuis, 2006). Additionally, the reduction in the LPP correlated with reductions in self-reported emotional experience following reappraisal (Hajcak et al., 2006). The amplitude of the LPP also appears sensitive to how attention is deployed within aversive stimuli: when attention is directed to more or less arousing aspects of unpleasant pictures, the amplitude of the LPP is increased and decreased, respectively (Hajcak et al., 2007a; Dunning and Hajcak, 2009). Moreover, manipulations that increase or decrease the aversiveness of visual stimuli have been shown to increase and decrease the LPP, respectively (Foti and Hajcak, 2008; Macnamara et al., 2009). In fact, the LPP elicited by neutral pictures can be increased through experimental manipulation that increase self-reported arousal and unpleasantness of neutral stimuli (Macnamara et al., 2009). We have argued that the LPP reflects increased attention-related neural activity in parietal networks that can be modulated by manipulations of attention, stimulus meaning, and regulatory efforts (Hajcak et al., 2010).

Despite evidence for PFC involvement in emotion regulation, there has been no direct evidence relating the activity in specific regions of the PFC to changes in electrocortical measures of visual attention. The dorsolateral (DL) prefrontal cortex maintains preferential bi-directional connections both with multimodal temporal areas, and paralimbic cortical areas such as the cingulate, the retrosplenial and the rostral temporal cortex (Petrides, 2005). The frontopolar (FP) prefrontal cortex is part of a distributed network extending caudally, now commonly referred to as the "default-mode" network (Raichle and Snyder, 2007) and has rich connections directed to the anterior cingulate cortex, precuneus and posterior cingulate (Goldman-Rakic, 1988), orbitofrontal and dorsolateral prefrontal cortex (Ramnani and Owen, 2004; Petrides and Pandya, 2007). Christoff and Gabrieli (2000) suggested a hierarchical model of prefrontal cortex function in which DL and FP cortex are involved in the processing of externally and internally generated information, respectively.

The current study focused on testing the causal impact of prefrontal cortex activation on the LPP using direct epidural cortical stimulation (Priori and Lefaucheur, 2007) of two bilateral regions of the PFC: the DL prefrontal cortex (Brodmann's areas 46) and the FP prefrontal cortex (Brodmann's area 10), as both regions offer a distinct opportunity to examine their potential impact on neural activity elicited by salient visual stimuli. We measured the LPP from a group of five patients with treatment-resistant mood disorders (TRMD) who had epidural stimulation paddles implanted bilaterally over FP and DL prefrontal cortex. Based on DL prefrontal cortex involvement in studies of emotion regulation and sensitivity of the LPP to emotion regulation instructions, we hypothesized that direct cortical stimulation of the DL prefrontal cortex will selectively reduce the amplitude of the LPP.

EXPERIMENTAL PROCEDURES

Recruitment/consent

The study was conducted at the Medical University of South Carolina in compliance with an Investigational Device Exemption issued to Dr. Nahas under US Food and Drug Administration guidance. The MUSC Institutional Review Board approved the protocol as part of a larger effort to test the feasibility and potential efficacy of epidural cortical stimulation (EpCS) in treatment resistant depression. Written consents were obtained in the presence of a patient advocate also independent of the study team.

Overall design

The full protocol of the EpCS study is detailed elsewhere, including specific data regarding treatment history and the placement of epidural stimulators (Nahas et al., 2010). In short, inclusion criteria limited enrollment to depressed participants with definite histories of substantial treatment resistance. Five patients underwent neurosurgical stereotactic implantation of four cortical stimulation paddle leads placed bilaterally over the frontopolar and mid-lateral prefrontal cortices. The accuracy of electrodes placement was confirmed with post-operative CT scans. This study reports on patients' first exposures to EpCS after a minimum 2-week post-operative recovery period. The stimulation was coupled with high-density 64-channel electroencephalograph (EEG) recordings and passive viewing of aversive and neutral images. Specifically, each participant viewed aversive and neutral pictures under blind conditions: sham stimulation, bilateral stimulation of BA10 at 2 V, bilateral stimulation of BA10 at 4 V, bilateral stimulation of BA46 at 2 V, and bilateral stimulation of BA46 at 4 V. Each condition was repeated two times (www.randomization.com).

Stimulus materials

Two sets of 80 pictures (160 total pictures) were selected from the International Affective Picture System (IAPS; Lang et al., 1999); within each set, 40 pictures depicted neutral scenes (e.g., neutral faces, household objects), and 40 depicted unpleasant scenes (e.g., sad faces, violence images).[1] For both sets of pictures, neutral and unpleasant pictures differed on normative ratings of valence, based on a 9-point scale with 1 being maximally unpleasant and 9 being maximally pleasant (Set 1:M=2.60, SD=.69 for unpleasant pictures; M=5.27, SD=.54 for neutral pictures. Set 2: M=2.57, SD=.74 for unpleasant pictures; M=5.23, SD=.57 for neutral pictures); additionally, the emotional pictures were reliably higher on normative arousal ratings (Set 1: M=6.11, SD=.61 for unpleasant pictures; and M=3.16, SD=.74 for neutral pictures. Set 2: M=6.08, SD=.61 for unpleasant pictures; and M=3.15, SD=.57 for neutral pictures).

The task was administered on a Pentium D class computer, using Presentation software (Neurobehavioral Systems, Inc.; Albany, CA, USA) to control the presentation and timing of all stimuli. The inter-trial interval varied randomly from 500 to 1000 ms; during this time, a white fixation cross was presented on a black screen. Each picture was then displayed in color for 1000 ms and occupied the entirety of a 19-in (48.26 cm) monitor. At a viewing distance of approximately 24 in. (60.96 cm), each picture occupied approximately 40° of visual angle horizontally and vertically.

Procedure

After a brief description of the experiment, EEG sensors were attached and the participant was given more detailed task instructions. Participants were told that they would be viewing pictures depicting a wide range of content, some pictures being neutral, and others being aversive or threatening. Participants were asked to focus on the screen and simply watch all of the pictures as they were displayed. All participants initially viewed a series of 10 practice pictures to accommodate them to the task. After the practice trials, participants performed 10 blocks of 80 trials; participants could take breaks between the blocks, and also received breaks after every 20 trials within each block. At the beginning of each block, an instruction reading "SIMPLY VIEW THESE PICTURES" was displayed on the screen for 1000 ms. The order of the trials was randomly determined within each block for each participant.

In each block, one of the sets of pictures (i.e., 40 neutral and 40 unpleasant) were presented in a random order. Each set of pictures was viewed in five conditions: during a sham (no stimulation) condition, while BA10 was stimulated at 2 V, while BA10 was stimulated at 4 V, while BA46 was stimulated at 2 V, and while BA46 was stimulated at 4 V. The first set of pictures was presented five times, once in each of the five conditions; then, the second set of pictures was presented five times, once in each of the five conditions. The order of stimulation conditions was randomized across participants. The subject was blind to the stimulation condition and stimulation began prior to the presentation of the first picture in the block and continued throughout the presentation of all pictures in the block. All stimulation was bilateral at 60 Hz, which was selected based on the ECS literature(Priori and Lefaucheur, 2007). Stimulation was terminated between all blocks during the break.

Psychophysiological recording and data reduction

The continuous EEG was recorded using the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Recordings were taken from 64 scalp electrodes based on the 10/20 system, as well as two electrodes placed on the left and right mastoids. The electrooculogram (EOG) generated from blinks and eye movements was recorded from four facial electrodes: two approximately 1 cm above and below the participant's right eye, one approximately 1 cm to the left of the left eye, and one approximately 1 cm to the right of the right eye. As per BioSemi's design, the ground electrode during acquisition was formed by the Common Mode Sense active electrode and the Driven Right Leg passive electrode.

All bioelectric signals were digitized on a laboratory microcomputer using ActiView software (BioSemi). The EEG was sampled at 512 Hz. Off-line analysis was performed using Brain Vision Analyzer software (Brain Products). All data were re-referenced to the average of all scalp electrodes; data were filtered using a high-pass filter set to .1 Hz, and a low-pass filter set to 20 Hz to eliminate all activity produced by the stimulators. The EEG was segmented for each trial, beginning 200 ms before each picture onset and continuing for 1200 ms (i.e., the duration of picture presentation). The EEG for each trial was corrected for blinks and eye movements using the method developed by Gratton, Coles, and Donchin (Gratton et al., 1983). Specific trials for individual channels were rejected using a semi-automated procedure, with physiological artifacts identified by the following criteria: a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100 ms intervals. All epochs were also inspected visually for any remaining artifact. ERPs were constructed by separately averaging trials for neutral and aversive pictures, as a function of stimulation condition—these averages were created by collapsing across the two picture sets. Thus, each participant had one ERP average for neutral and unpleasant trials in all five conditions: sham, BA10 stimulated at 2 and 4 V, and BA10 stimulated at 2 and 4 V. In each case, the average activity in the 200-ms window prior to picture onset served as the baseline.

Based on previous research indicating that the LPP is typically maximal at posterior and parietal sites (Schupp et al., 2000; Keil et al., 2002; Hajcak et al., 2007a; Foti and Hajcak, 2008), the LPP was quantified as the average activity at a centro–parietal pooling (i.e., Pz, P1, P3, PO3, PO4, and POz) in a window extending from 400 to 1000 ms after picture presentation (Foti et al., 2009, for factor analytic work on spatial and temporal characterization of the LPP). The LPP amplitudes for each subject were converted to *T*-scores to reduce between-subject variability unrelated to the within-subjects variables of interest. The LPP was first evaluated during the passive viewing blocks using a paired-samples *t*-test to confirm that patients in the current study demonstrated typical LPPs to aversive compared to neutral pictures. Next, the LPP was evaluated using a 2 (Stimulation Site: FP (BA 10), DL (BA 46))×2 (Stimulation Intensity: 2 V, 4 V) repeated-measures ANOVA. In all cases, the LPP was statistically evaluated using SPSS (Version 15.0) General Linear Model software.

[1] The IAPS pictures used were neutral 1450, 1910, 2191, 2357, 2394, 2514, 2575, 2620, 2840, 5395, 5250, 5455, 5532, 5520, 5731, 5900, 7000, 7004, 7006, 7950, 7700, 7590, 7550, 7546, 7491, 7235, 7504, 7039, 7175, 7150, 7090, 7035, 7037, 7041, 7043, 7211, 7217, 2190, 2104, 5800, 1670, 2038, 2235, 2320, 2393, 2580, 2593, 2745.1, 2870, 5390, 5130, 5471, 5533, 5510, 5740, 5875, 7002, 7009, 7010, 7705, 7595, 7560, 7493, 7547, 7500, 7025, 7236, 7130, 7140, 7100, 7080, 7030, 7038, 7034, 7050, 7190,7058, 2206, 2200, 5764; and unpleasant1120, 1205, 1301, 1321, 2053, 2130, 2703, 2710, 2691, 2800, 3261, 6190, 6250, 6230, 6510, 6313, 6550, 6300, 6242, 6560, 6571, 6831, 6836, 9050, 9902, 9903, 9911, 9635.1, 9925, 9592, 9600, 9250, 9252, 9300, 9405, 9433, 9425, 9400, 3010, 3053, 1050, 1200, 1303, 1930, 2661, 2120, 2095, 2717, 2683, 3030, 3225, 6200, 2811, 6260, 6370, 6312, 6350, 6540, 6243, 6570, 6555, 6838, 6834, 9810, 9901, 9900, 9910, 3005.1, 9921, 9594, 9620, 9254, 9253, 9301, 9410, 9470, 9426, 9520, 3051, 3170.

Table 1. Subject demographics, clinical characteristics, and standardized LPP values for each condition (and standard deviations)

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Group
Gender	F	M	F	F	F	4 F/1 M
Diagnosis	Recurrent MDD	BPAD depressed	BPAD depressed	Recurrent MDD	Recurrent MDD	3 MDD/2 BPAD
Current age	42	57	47	31	45	44.4 (9.7)
Length of illness (y)	17	32	31	16	32	25.6 (8.3)
Current episode (mon)	31	83	84	8	8	42.8 (38.3)
Hamilton depression score (24 item)	22	32	38	29	28	29 (5.8).
Previous brain stimulation therapies	ECT, VNS and TMS	ECT, VNS and TMS	ECT	VNS and TMS	None	4 Yes/1 No
Past psychotherapy	Yes	Yes	Yes	Yes	Yes	All
Family history of depression	Yes	Yes	No	Yes	Yes	4 Yes/1 No
Number of psychiatric treatments in current depressive episode	12	18	6	8	5	9.8 (5.3)
Current ATHF	8	8	4	5	4	5.8 (2.05)
Number of psychotropics at baseline	9	5	6	3	7	6 (2.23)
Standardized LPP (neutral)						
Sham	36.20	36.81	49.40	42.68	38.17	40.65 (2.26)
BA 10/2 V	41.43	42.50	37.43	43.62	44.02	41.80 (2.11)
BA 10/4 V	44.17	43.57	46.38	34.65	47.00	43.16 (2.91)
BA 46/2 V	42.18	41.80	43.27	46.70	36.64	42.12 (3.59)
BA 46/4 V	46.20	40.40	35.29	46.37	44.90	42.63 (2.13)
Standardized LPP (aversive)						
Sham	61.50	54.58	64.00	65.74	55.29	60.22 (2.46)
BA 10/2 V	58.98	61.43	60.30	63.08	50.94	58.95 (1.18)
BA 10/4 V	67.55	61.20	56.22	53.45	67.87	61.26 (2.22)
BA 46/2 V	52.32	63.02	60.79	44.48	62.44	56.61 (1.62)
BA 46/4 V	49.44	54.72	46.92	59.23	52.73	52.61 (2.13)

RESULTS

Sample characteristics

No participant was able to tell sham from stimulation conditions. Table 1 summarizes the sample characteristics. The mean age was 44.2 (±9.4). Four patients were women and three were diagnosed with recurrent Major Depressive Disorder whereas two others had Bipolar Affective Disorder I, depressed type. All were unemployed and three were receiving disability. The average length of depressive illness was 25.6 (±8.3) years. The average length of the current depressive episode was 3 years, 7 months (±38 months). Four of the patients received prior treatments with electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) and vagal nerve stimulation (VNS). The most recent exposure to a brain stimulation technology other than EpCS was to TMS 4 months earlier. They enrolled in the study taking on average 6 (±2.3) psychotropic drugs.

LPP during sham

Standardized LPP scores for each subject, for aversive and neutral pictures in the sham condition, are presented in Table 1. Fig. 1 (left) presents the scalp distribution of the ERP difference between aversive and neutral pictures from 400 to 1000 ms following stimulus presentation during the sham condition. The ERP elicited by neutral and aversive pictures at centro–parietal recording sites in the sham condition is presented in Fig. 1 (middle): the LPP is evident as a sustained increase in the stimulus-locked positivity for unpleasant compared to neutral pictures. The impression from Fig. 1 was confirmed statistically: the parietally-maximal positivity was larger for aversive than neutral pictures ($t(4)=9.85$, $P<.001$, $\eta_p^2=.96$).

LPP during PFC stimulation

Standardized LPP scores for each subject, in each of the stimulation conditions for aversive and neutral pictures are presented in Table 1. Fig. 2 presents standardized LPP amplitudes elicited by aversive (left) and neutral (right) pictures as a function of stimulation site and intensity; the amplitude of the LPP during the sham condition is represented by the horizontal dotted line. Overall, the LPP was larger for aversive than neutral pictures during stimulation ($F(1,4)=232.07$, $P<.001$, $\eta_p^2=.98$) and the electrocortical response to pictures was smaller overall when BA46 was stimulated ($F(1,4)=8.15$, $P=.048$, $\eta_p^2=.67$). The relatively large reduction in LPP amplitude during BA46 stimulation for unpleasant compared to a small increase in LPP during neutral pictures did not reach significance ($F(1,4)=2.35$, $P>.20$, $\eta_p^2=.37$). The effect of stimulation intensity and all other two- and three-way interactions did not reach signif-

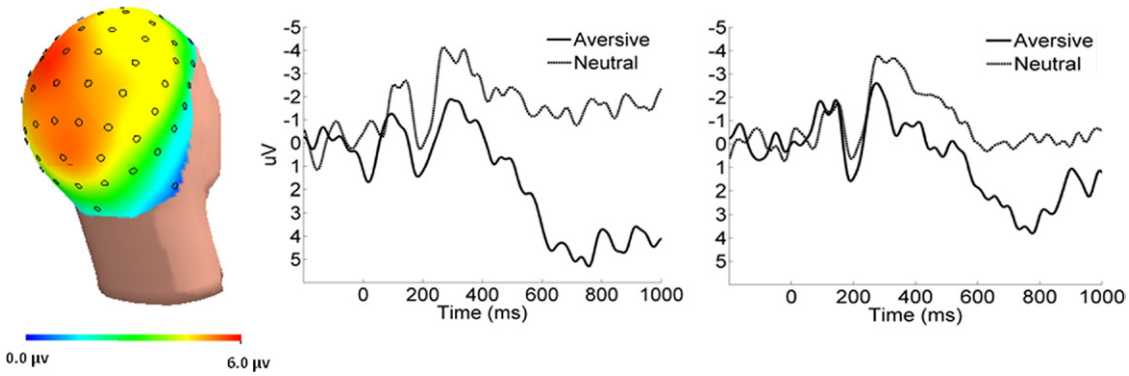

Fig. 1. Scalp distribution of the ERP difference between aversive and neutral pictures from 400 to 1000 ms following picture presentation (left); ERPs at centro–parietal recording sites time-locked to picture onset (middle, right) for aversive (dark) and neutral (light) trials during the sham condition (middle) and when BA46 was stimulated at 4 volts (right). Picture onset occurred at 0 ms and negative is plotted up. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

icance (all $Fs<1$). Based on initial findings, we conducted exploratory post hoc paired-sample *t*-tests in which we compared the sham condition to each stimulation condition, separately for neutral and aversive pictures. At a liberal statistical threshold, the only condition that differed from sham was aversive pictures presented while BA46 was stimulated at 4 V ($t(4)=2.43$, $P<.05$, one-tailed); all other comparisons did not reach significance (all $Ps>.50$). Fig. 1 (right) presents the ERPs elicited by neutral and aversive images while BA46 (i.e., DL prefrontal cortex) was stimulated at 4 V, and demonstrates the relatively reduced neural differentiation between aversive and neutral images in this condition.

DISCUSSION

To our knowledge, this is the first report of direct epidural cortical stimulation and its effects on electrocortical measures of visual attention. Treatment-resistant mood disorder patients in the current study were characterized by a normative increase in the LPP in response to emotional compared to neutral pictures in the sham condition. Moreover, only bilateral EpCS of the DL prefrontal cortex (BA 46) was associated with a reduction in the LPP. In the primary analysis, this effect was not specific to aversive pictures; however, exploratory analyses suggested that DLPFC stimulation led to a more robust reduction in the LPP to aversive images at higher stimulation intensity, although this finding should be interpreted with caution as liberal statistical thresholds were used.

Functionally, the LPP appears to reflect increased visual attention to motivationally salient environmental stimuli (Bradley et al., 2003; Schupp et al., 2004b, 2007). In support of this possibility, we have recently found that increased attention to task irrelevant pictures indexed by larger LPPs predicted longer RTs to subsequently presented targets (Weinberg and Hajcak, in press). Moreover, the amplitude of the LPP varies when the salience of both aversive and neutral stimuli is emphasized through both meaning-based (Foti and Hajcak, 2008; Macnamara et al., 2009) and attentional manipulations (Hajcak et al., 2007a; Dunning and Hajcak, 2009).

The current study suggests that direct stimulation of the DL prefrontal cortex also reduces the amplitude of the LPP. In this way, activation of the DL prefrontal cortex may

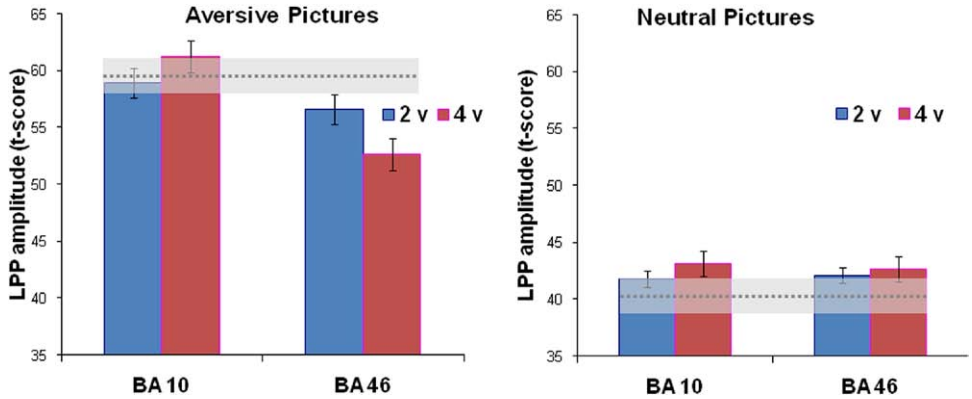

Fig. 2. LPP amplitude for aversive (left) and neutral (right) pictures presented while BA 10 and BA 46 were stimulated at 2v and 4v. The dotted horizontal line represents the LPP amplitude during the no simulation baseline condition. Error bars and shaded area around the sham condition mean reflect the standard error of the mean. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

serve to modulate parietal attentional networks involved in the automatic processing of salient environmental stimuli. Moreover, these data suggest regional specificity in the modulation of ERP correlates of visual attention: the lateral prefrontal cortex appears to play a more direct and prominent role in immediately regulating attention and reactivity to external stimuli than the rostral prefrontal cortex (i.e., BA 10).

There is a growing literature that documents DL prefrontal cortex involvement in successful emotion regulation (Beauregard et al., 2001; Ochsner et al., 2002; Levesque et al., 2003; Phan et al., 2005; Banks et al., 2007; Eippert et al., 2007; Johnstone et al., 2007). A recent study demonstrated an inverse correlations between amygdala and lateral, but not medial, PFC (Roy et al., 2009). In light of these data, the current results suggest that DL prefrontal cortex might be involved in the more general regulation of attention (Wager et al., 2004). Along these lines, future studies may wish to evaluate whether DL prefrontal cortex stimulation similarly reduces attention-related ERPs such as the P300 in non-emotional contexts, and whether such effects are consequent to direct activation of large fronto–parietal white matter bundles (Mori et al., 2008) as opposed to modulation of sub-cortical limbic regions.

In addition to providing evidence regarding the modulatory role of the DL prefrontal cortex in parietal attention networks, the current results also suggest a mechanistic foundation for why lateral PFC EpCS might successfully treat depression (Dougherty et al., 2008; Nahas et al., 2010). Three of these five patients showed complete remission of symptoms after 7 months of treatment. Specifically, whether direct EpCS DL prefrontal cortex stimulation may strengthen cortico-limbic regulating circuits (Alexander et al., 1986) and reduce the intensity or frequency of exaggerated responses to stimuli remains to be explored.

An obvious limitation of the current study is the small sample and unique patient selection. EpCS is a neurosurgical procedure where leads are placed through a burr hole in the skull but above the dura mater, and thus the leads remain separated from the underlying cortical region by the arachnoid space. It is therefore reserved for patients resistant to more benign treatment options. Whether the current results would generalize to non-TRMD patients remains to be determined. However, TMS may offer an alternative for testing such hypotheses in various populations including healthy adults (Hajcak et al., 2007b). Another clear limitation of the present study is the relatively low number of participants, and resulting low statistical power. Determining whether stimulation of DL prefrontal cortex parametrically reduces physiological measures of attention and emotional reactivity—and specificity for aversive stimuli—will require larger samples. Additionally, it is possible that the optimal voltage and stimulation frequency were not used in the current study—which may have contributed to the failure to find an effect of FP prefrontal cortex stimulation on ERP measures. Nonetheless, the present data provide important initial data that might guide future studies in an area where large samples are both difficult and costly to recruit.

CONCLUSION

In summary, this study provides unique support for the role of DL prefrontal cortex in reducing neural activity that has previously been linked to increased visual attention and perceptual processing of salient stimuli (Hajcak et al., 2010). Given the FP prefrontal cortex's role in self-referential processing, future studies should explore whether its stimulation selectively impacts more internally generated emotional experience.

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