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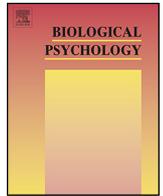
Neural markers of attention to aversive pictures predict response to cognitive behavioral therapy in anxiety and depression[☆]

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ABSTRACT

Excessive attention toward aversive information may be a core mechanism underlying emotional disorders, but little is known about whether this is predictive of response to treatments. We evaluated whether enhanced attention toward aversive stimuli, as indexed by an event-related potential component, the late positive potential (LPP), would predict response to cognitive behavioral therapy (CBT) in patients with social anxiety disorder and/or major depressive disorder. Thirty-two patients receiving 12 weeks of CBT responded to briefly-presented pairs of aversive and neutral pictures that served as targets or distracters while electroencephaolography was recorded. Patients with larger pre-treatment LPPs to aversive relative to neutral distracters (when targets were aversive) were more likely to respond to CBT, and demonstrated larger reductions in symptoms of depression and anxiety following treatment. Increased attention toward irrelevant aversive stimuli may signal attenuated top-down control, so treatments like CBT that improve this control could be beneficial for these individuals.

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1. Introduction

Social anxiety disorder (SAD) and major depressive disorder (MDD) are prevalent, frequently comorbid and highly impairing (Kessler et al., 2003, 2005, 2006; Mineka, Watson, and Clark, 1998; Beesdo et al., 2007; Kaufman & Charney, 2000; Stein et al., 2001). Excessive attention toward aversive information has been proposed as a core mechanism underlying these emotional disorders (Mathews & MacLeod, 2005; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). Cognitive-behavioral therapy (CBT) is a gold-standard psychosocial treatment for anxiety and depressive disorders that targets emotional disorders by facilitating coping with aversive emotions, and that may change how threat is processed (Beck, Rush, Shaw, & Emery; Hofmann et al., 2012). Although CBT has demonstrated moderate effectiveness for emotional disorders, not all patients benefit equally from CBT, and many patients remain symptomatic after an initial intervention (Hofmann & Smits, 2008; Kemp, Gordon, Rush, Williams, 2008). Identifying patient characteristics associated with response to CBT may lead to more personalized treatment decision-making (Paulus, 2015).

Given the extremely high rates of comorbidity between SAD and MDD, it is likely that common factors, such as heightened negative affectivity and increased attention toward negative environmental information, may underlie both disorders (Gibb, McGeary, Beevers, 2015; Mathews & MacLeod, 2002; Pessoa, Kastner, & Ungerleider, 2002). As a result, CBT involves similar treatment strategies for SAD and MDD, including cognitive restructuring about real or potential negative situations, and encouraging exposure to environmental situations that are perceived as negative or undesirable (Beck & Bredemeier, 2016; Rodebaugh, Holaway, & Heimberg, 2004). Reducing the salience of negative emotional or environmental stimuli that interfere with situational goals thus is one aim of treat-

ment, and the degree to which such stimuli are salient could serve as an indicator of which patients are most likely to benefit from CBT.

Given the possibility of partially overlapping mechanisms of illness, it will be important to identify common factors predicting treatment response across SAD and MDD. One potential predictor of treatment response is increased attention toward aversive stimuli (Eysenck, 1992; Mathews & MacLeod, 2002; Peckham, McHugh, & Otto, 2010; Gibb et al., 2015; Pessoa et al., 2002). Elevated salience of aversive stimuli may lead to excessive bottom-up processing of goal-irrelevant, sensory-driven stimuli, at the expense of top-down control to attend to the goal at hand (Pessoa et al., 2002). Increased attention to aversive stimuli has been found across multiple emotional disorders (Bar-Haim et al., 2007), including SAD (Kircanski, Joormann, & Gotlib, 2015) and MDD (Peckham et al., 2010; but see Weinberg, Perlman, Kotov, & Hajcak, 2016; Kircanski et al., 2015). Neural measures, such as functional magnetic resonance imaging (fMRI), provide promising tools for assessing attention to aversive stimuli (Doehrmann et al., 2013; Klumpp, Fitzgerald, & Phan, 2013; Fu et al., 2008; Whalen et al., 2008). In comparison to fMRI, event-related potentials (ERPs) such as the late positive potential (LPP), assessed by EEG, provide a less expensive and clinically practical means of elucidating the processing of negatively-valenced information in emotional disorders (Bar-Haim, Lamy, & Glickman, 2005; Hajcak, Weinberg, MacNamara, & Foti, 2012; MacNamara et al., 2011, 2013). Prior work has demonstrated that the LPP to aversive stimuli is elevated among individuals with anxiety disorders (MacNamara & Hajcak, 2010; Li, Zinbarg, & Paller, 2007), with or without the presence of comorbid depression (Dillon et al., 2014; MacNamara & Proudfit, 2014; Brown, 2007; Desseilles et al., 2009, 2011). A more limited literature in depression has suggested that depression without anxiety may be characterized by attenuated LPPs to motivationally-salient stimuli (Proudfit et al., 2015). Thus, measurement of the attentional processing of aversive stimuli using the LPP may help to elucidate the neural mechanisms underlying SAD and MDD (e.g., Gibb et al., 2015), and could serve as useful measures of propensity to benefit from treatment.

Despite evidence that shared mechanisms may underlie SAD and MDD (Dillon et al., 2014; Mineka et al., 1998) and increasing interest in understanding neural predictors of treatment response (Andreescu & Aizenstein, 2016; Paulus, 2015) across traditional diagnostic groups (Cuthbert, 2014), limited work has evaluated whether brain-based measures of attention to aversive stimuli prior to treatment could predict response to CBT for these disorders. Prior work has suggested that response to treatment for anxiety and depression is associated with reductions in attention toward aversive stimuli (Etkin & Schatzberg, 2011; Pishyar, Harris, & Menzies, 2008); therefore, neural activity associated with attention toward aversive stimuli might be helpful in predicting who is most likely to benefit from such treatments (e.g., Doehrmann et al., 2013; Klumpp et al., 2013, 2014). In line with this hypothesis, prior neuroimaging work has demonstrated that greater higher-order visual cortex activation for negative stimuli prior to treatment predicted better response to CBT for social anxiety (Doehrmann et al., 2013; Klumpp et al., 2013). Other studies have found that response to CBT was predicted by greater pre-treatment reactivity in prefrontal cortical areas in youth with anxiety disorders (Kujawa et al., 2016), in rostral anterior cingulate cortex (ACC) to fearful faces among adults with generalized anxiety disorder (Whalen et al., 2008), and in dorsal ACC activity to sad faces among depressed adults (Fu et al., 2008). Furthermore, simultaneous fMRI/EEG studies have suggested that activation in these regions (particularly the visual cortices) may represent a key neural source contributing to the LPP elicited by aversive stimuli (Liu et al., 2012; Sabatinelli, Lang, Keil, & Bradley, 2007); however, few studies have evaluated the LPP – a relatively cost-effective and well-tolerated neural measure – as a predictor of treatment outcome in the anxiety and depressive disorders. One extant study of individuals with spider phobia (Leutgeb, Schäfer, & Schienle, 2009) found treatment-related increases in the LPP for aversive stimuli, suggesting that a higher LPP to aversive stimuli may be indicative of less avoidance (e.g., a willingness to engage with aversive stimuli; Weinberg & Hajcak, 2011) and better outcomes. Few studies of depression have evaluated the LPP as a predictor of treatment outcome. However, neuroimaging studies have found evidence that greater pre-treatment activation in the amygdala (Canli et al., 2005; Siegle, Carter, & Thase, 2006) and the temporal cortex (Ritchey et al., 2011) is associated with an improved course of depressive symptoms and greater response to CBT. Together, these results suggest that individuals who show neural correlates of enhanced attention toward aversive, goal-irrelevant stimuli may be particularly likely to benefit from CBT.

In the present study, we evaluated whether individual differences in attention to aversive stimuli (as indexed by the LPP) presented in attended or unattended locations would be associated with reduced illness severity following CBT for SAD or MDD, using a task previously shown to differentiate individuals with anxiety from those without (MacNamara & Hajcak, 2009, 2010). As in prior work (MacNamara & Hajcak, 2009, 2010), we expected that LPPs would be greater for aversive stimuli than for neutral stimuli when presented in attended locations, but not when stimuli were presented in unattended locations. Given prior work demonstrating that greater LPPs to aversive stimuli are associated with anxiety (MacNamara & Hajcak, 2009, 2010), and fMRI results suggesting that greater attention to aversive stimuli is associated with improved CBT outcomes (Doehrmann et al., 2013; Canli et al., 2005; Fu et al., 2008; Klumpp et al., 2013; Kujawa et al., 2016; MacNamara & Hajcak, 2010; Siegle et al., 2006; Whalen et al., 2008), we hypothesized that individuals with larger LPPs to aversive stimuli would be more likely to respond to CBT, and would show larger decreases in symptoms of anxiety and depression, relative to individuals with smaller LPPs to aversive stimuli. Given that prior work demonstrated associations between anxiety and attention to aversive targets (MacNamara & Hajcak, 2009, 2010), we expected that greater attention to aversive targets would predict better treatment outcome; we did not have a priori hypotheses about whether treatment outcome would be associated with LPPs to aversive distracters. Distracters were included in prior studies using this task and in the current study to explore whether attention to aversive stimuli would predict treatment response differentially as a function of the relevance of the stimuli to the current goal (i.e., attending to targets, not distracters).

2. Method

2.1. Participants

All participants met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a current diagnosis of social anxiety disorder or major depressive disorder (see Table 1). All participants were free of psychotropic medication for at least 8 weeks prior to, and throughout, the study. Exclusion criteria were as follows: a) substance abuse or dependence in the prior six months, b) history of bipolar disorder or schizophrenia, or the presence of an organic mental syndrome, intellectual disability, or pervasive developmental disorder, c) ongoing psychotherapy and/or current treatment with any psychotropic medication, and d) clinically significant medical or neurologic condition. Participants were between 18 and 55 years of age and right-handed. The study protocol was approved by the Institutional Review Boards of the University of Michigan Medical School and the University of Illinois at Chicago, and all participants provided written informed consent.

Table 1
Sample characteristics and diagnoses.

	Mean	SD
Age (years)	24.03	5.38
Education (years)	15.22	2.20
	N	%
Female	27	84.4
Race		
Caucasian	19	59.4
African American	1	3.1
Asian	8	25.0
More than one race	4	12.5
Hispanic or Latino/a	7	21.9
Primary Diagnosis		
Social Anxiety Disorder	20	62.5
Major Depressive Disorder	12	37.5
Any Current Diagnosis		
Social Anxiety Disorder	26	81.3
Major Depressive Disorder	13	40.6
Generalized Anxiety Disorder	9	28.1
Panic Disorder	8	25.0
Specific Phobia	3	9.4
Post-Traumatic Stress Disorder	4	12.5

Note. N = 32. CGI = Clinical Global Impression scale; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale.

2.2. Materials and measures

2.2.1. Diagnostic interview

Participants were interviewed by Master's- or Doctoral-level clinicians using the Structured Clinical Interview for DSM-IV (SCID-IV) (First, Spitzer, Gibbon, & Williams, 1996) to assess Axis I disorders (see Table 1).

2.2.2. Treatment outcome measures

To assess illness severity and response to CBT, clinicians completed the Clinical Global Impression (CGI) Severity and Improvement scales (Busner & Targum, 2007). Both measures use 7-point scales, ranging from 1 (normal, not at all ill) to 7 (extremely ill) for CGI Severity and from 1 (very much improved) to 7 (very much worse) for CGI Improvement. As in prior work (Barlow, Gorman, Shear, & Woods, 2000), we used the CGI-Severity and CGI-Improvement scales in conjunction to determine degree of treatment response. Participants with scores < 3 on both scales were determined to have achieved clinically-significant treatment response and were categorized as "Responders," while those with scores ≥ 3 were classified as "Non-Responders."

The 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960), a widely-used interview-based measure of depression symptom severity and the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959), a 14-item clinician-administered measure of severity of anxious symptomatology, were administered by trained, independent evaluators at pre- and post-treatment to assess changes in symptoms of depression and anxiety, respectively.

2.2.3. Affective pictures

Forty-eight aversive (e.g., attack scenes, mutilated bodies) and 48 neutral pictures (e.g., household objects, neutral faces) were selected from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2005). In prior studies validating this task, aversive pictures were rated as less pleasant and higher in arousal than neutral pictures (see MacNamara & Hajcak, 2009; for details). Stimuli were presented on a Dell Optiplex 750 computer, using Presentation software (Neurobehavioral Systems, Inc.). Participants were seated approximately 60 cm from the screen.

2.3. Procedures

2.3.1. CBT

Patients received 12 weeks of manualized, individual CBT conducted by doctoral-level clinical psychologists (Beck et al., 1979; Craske, Barlow, & O'Leary, 1992; Hope, Heimberg, & Turk, 2006; Martell, Dimidjian, & Herman-Dunn, 2010). A licensed clinical psychologist with expertise in CBT and in clinical trial investigations involving CBT provided supervision to ensure adherence to treatment. CBT included psychoeducation, cognitive restructuring, in vivo exposures, behavioral activation, and relapse prevention. The specific type of CBT provided was targeted toward each patient's primary diagnosis.

2.3.2. Affective picture task

Pre-treatment, participants completed a computerized task while EEG was recorded. In brief, four Pictures – two to the left and right, and two above and below the center of the screen – were presented simultaneously on each trial; participants were asked to indicate whether two of the pictures (either the vertical or horizontal picture pairs) were the same or different. Picture valence (aversive or neutral) was always the same in both the horizontal and vertical pairs. From here on, stimuli presented in task-relevant spatial locations will be referred to as "targets," and those presented in task-irrelevant locations will be referred to as "distracters."

There were four trial types: neutral targets paired with neutral distracters, neutral targets paired with aversive distracters, aversive targets paired with neutral distracters, and aversive targets paired with aversive distracters. Participants used the left and right mouse buttons (counterbalanced across participants) to indicate if targets were identical ("same") or different ("different"); participants were encouraged to respond as quickly and as accurately as possible. Before each trial, two white rectangles appeared on a black background for 1000 ms to indicate which picture pair (horizontal or vertical) would be the targets for the same/different decision in the upcoming trial; pictures were displayed in color for 250 ms. Participants completed 10 practice trials and 320 experimental trials. Pictures presented during practice trials were not repeated during experimental trials. Trial order and pictures were presented pseudo-randomly, with each picture repeated 10 times across the task (for more details see MacNamara & Hajcak, 2009).

2.4. Electroencephalographic recording and behavioral responses

An elastic cap and the ActiveTwo BioSemi system (Amsterdam, Netherlands) were used to record the continuous EEG. Thirty-four electrode sites (standard 32 channel setup plus Iz and FCz) based on the 10/20 system, were used, with one additional electrode on each of the left and right mastoids. Four facial electrodes recorded the electrooculogram generated from eye blinks and eye movements: vertical eye movements and blinks were measured with two electrodes placed approximately 1 cm above and below the right eye; horizontal eye movements were measured with two electrodes placed approximately 1 cm beyond the outer edge of each eye. Online data were referenced according to BioSemi's design using two separate electrodes for grounding (the Common Mode Sense active electrode and the Driven Right Leg passive electrode) and data were digitized at 1024 Hz.

Off-line analyses were performed using Brain Vision Analyzer (Brain Products, Gilching, Germany); data were re-referenced to the average of the two mastoids and were band-pass filtered with low and high cutoffs of 0.01 and 30 Hz, respectively. The baseline for each trial was defined as the 200 ms before picture onset. ERPs were segmented for each trial beginning 200 ms before picture onset until 1200 ms (1000 ms beyond picture onset). Eye blink and ocular corrections were made using the algorithm developed by Miller,

Gratton, and Yee (1988). Artifact analysis identified a voltage step of more than 50 μV between sample points, a voltage difference of 300 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100 ms intervals. Trials were also inspected visually for any remaining artifacts. Intervals containing artifacts were rejected from individual channels in each trial. As in prior work, the LPP was scored by averaging activity from 400 to 1000 ms at four centro-parietal sites where the LPP was maximal: CP1, CP2, Cz, and Pz (e.g., Weinberg & Hajcak, 2010; Hajcak, Dunning, & Foti, 2007). Averages of LPPs for each trial type (80 trials in each of the four conditions noted above) were created for each participant. Only trials associated with a correct response made within 1800 ms following picture offset were included in the ERP analyses. The average reaction time (RT) per condition was determined as the average time taken to respond following picture onset on correct trials and accuracy was assessed as the percentage of correct responses per condition.

Participants generally performed well on the task ($M = 89.44\%$ correct, $SD = 8.84\%$). One (female) participant was removed from analyses because of excessive EEG artifacts (>50% of trials excluded), and two participants (one male, one female) were excluded because of poor task performance (less than 50% accuracy), yielding a final sample of $n = 32$ for analyses.

2.5. Statistical analyses

Task effects on the LPP, reaction time, and accuracy were evaluated with 2 (target type: neutral, aversive) x 2 (distracter type: neutral, aversive) repeated-measures analyses of variance (ANOVAs). To evaluate whether attention to aversive stimuli at pre-treatment predicted treatment outcome, we performed three analyses of covariance (ANCOVA). First a 2 (target type: neutral, aversive) x 2 (distracter type: neutral, aversive) ANCOVA was conducted, with pre-treatment CGI-Severity entered as a covariate of no interest, and post-treatment CGI Responder status as a covariate of interest. Next, we conducted the same 2 × 2 ANCOVA, but with pre-treatment HAM-D scores (instead of CGI-Severity) entered as a covariate of no interest, and post-treatment HAM-D (instead of CGI Responder status) as a continuous covariate of interest. Finally, we conducted the same 2 × 2 ANCOVA, this time controlling for pre-treatment HAM-A scores (as a covariate of no interest), and with post-treatment HAM-A as a continuous covariate of interest.

To follow up on significant ANCOVAs, post-hoc tests involved regressions for each of the four possible pairwise comparisons between trial types, predicting post-treatment symptoms (linear regressions) or recovery status (logistic regression): (1) aversive minus neutral distracter when targets were neutral; (2) aversive minus neutral distracter when targets were negative; (3) aversive minus neutral target when distracters were neutral); and (4) aversive minus neutral target when distracters were aversive.

3. Results

Sample demographics and clinical characteristics are detailed in Table 1.

3.1. Changes in clinical measures across treatment

CGI-Severity scores decreased from pre-treatment to post-treatment ($t(31) = 6.80$, $p < 0.001$, $d = 1.50$; Table 1). Based on the conservative approach of combining CGI-Severity and CGI-Improvement indices to determine treatment response (per Barlow et al., 2000), 36% of the sample (14 of 39 patients) were classified as Responders (i.e., rated "normal, not at all ill" or "borderline mentally ill" at post-treatment on CGI-Severity and "very much improved"

Table 2
Treatment outcome scores according to CGI responder status.

	Responder		Non-Responder	
	Mean	SD	Mean	SD
CGI Severity (pre-treatment)	4.00	0.00	4.36	0.57
CGI Severity (post-treatment)	1.64	0.50	3.57	0.75
CGI Improvement (post-treatment)	1.00	0.00	2.67	0.97
HAM-A (pre-treatment)	13.73	9.13	17.10	7.64
HAM-A (post-treatment)	2.82	2.82	8.67	5.08
HAM-D (pre-treatment)	8.55	6.70	11.00	6.82
HAM-D (post-treatment)	1.64	1.36	5.57	4.74

Note: $N = 32$. CGI = Clinical Global Impression scale; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale.

or "much improved" at post-treatment). Patients' primary diagnosis was not significantly associated with treatment responder status (SAD primary: $n = 12$ responders (57.1%); MDD primary: $n = 3$ responders (33.3%); $\chi^2(1) = 0.75$, $p = 0.39$). There were also significant decreases in HAM-D ($t(31) = 5.20$, $p < 0.001$, $d = 1.05$) and in HAM-A ($t(31) = 7.25$, $p < 0.001$, $d = 1.35$) from pre-treatment to post-treatment. Symptom scores as a function of CGI responder status are displayed in Table 2. At baseline, CGI responders had greater severity on the CGI ($t(20) = 2.86$, $p = 0.01$, $d = 0.89$).

3.2. Task effects

Fig. 1a depicts grand-average waveforms for each of the four trial types at centro-parietal sites where the LPP was scored (i.e., the average of CP1, CP2, Cz, and Pz); Fig. 1b displays scalp distributions for each trial type, from 400 to 1,000 ms post-picture onset. As expected based on prior work (MacNamara & Hajcak, 2009, 2010), there was a significant effect of target type on the LPP ($F(1,31) = 29.86$, $p < 0.001$, $\eta_p^2 = 0.49$), such that larger LPPs were elicited for aversive ($M = 4.64\,\mu V$, $SD = 4.27\,\mu V$) relative to neutral targets ($M = 2.53\,\mu V$, $SD = 4.15\,\mu V$). However, there was no main effect of distracter type ($F(1,31) = 0.04$, $p = 0.95$, $\eta_p^2 = 0.0001$; aversive $M = 3.57\,\mu V$, $SD = 4.19\,\mu V$; neutral $M = 3.60\,\mu V$, $SD = 4.20\,\mu V$), nor was there an interaction between target and distracter type ($F(1,31) = 0.05$, $p = 0.82$, $\eta_p^2 = 0.002$).

In terms of RT for accurate trials, there was a marginal main effect of target type ($F(1,31) = 3.30$, $p = 0.08$, $\eta_p^2 = 0.10$) such that aversive targets ($M = 687.03$ ms, $SD = 104.95$ ms) were associated with longer RTs than neutral targets ($M = 679.53$ ms, $SD = 104.81$ ms). The main effect of distracter type was not significant ($F(1,31) = 0.24$, $p = 0.63$, $\eta_p^2 = 0.008$), but there was a significant interaction between target and distracter type ($F(1,31) = 8.91$, $p < 0.01$, $\eta_p^2 = 0.22$; neutral targets with neutral distracters: $M = 668.36$ ms, $SD = 110.15$ ms; neutral targets with aversive distracters: $M = 672.70$ ms, $SD = 102.46$ ms; aversive targets with neutral distracters: $M = 682.21$ ms, $SD = 105.43$ ms; aversive targets with aversive distracters: $M = 691.85$ ms, $SD = 106.16$ ms). Post-hoc comparisons revealed that when targets were negative, negative distracters were associated with longer RTs ($p = 0.05$), whereas when targets were neutral, negative distracters were associated with shorter RTs ($p = 0.04$). When distracters were negative, negative targets were associated with longer RTs ($p < 0.01$), whereas when distracters were neutral, distracter valence was not associated with RT ($p = 0.39$). No significant effects were observed for accuracy (all $ps > 0.24$).

3.3. Treatment response prediction

Fig. 2 depicts LPP amplitudes for all conditions and spatial distributions for aversive relative to neutral distracters (under conditions of aversive targets) for Non-Responders (Fig. 2a) and
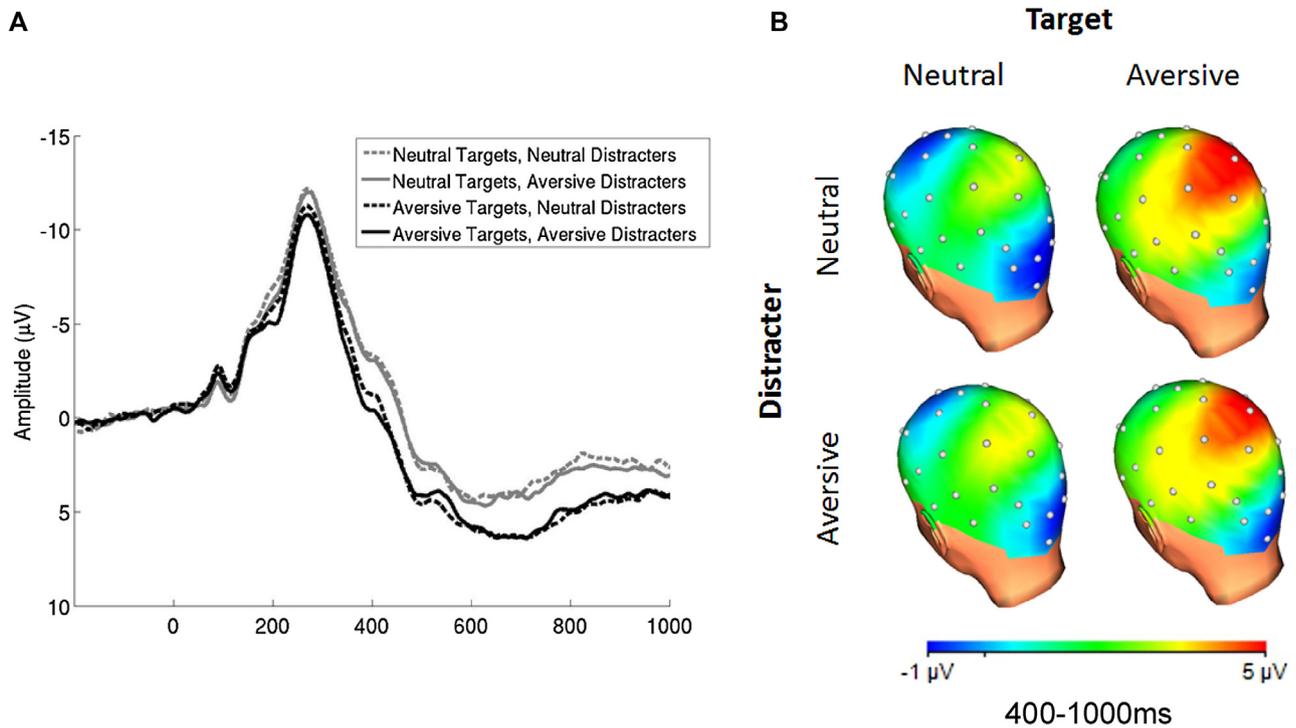
Fig. 1. Grand average amplitudes at pooling of CP1, CP2, Cz, and Pz (panel A) and scalp distributions of amplitudes from 400 to 1000 ms after picture onset (panel B) for each trial type.
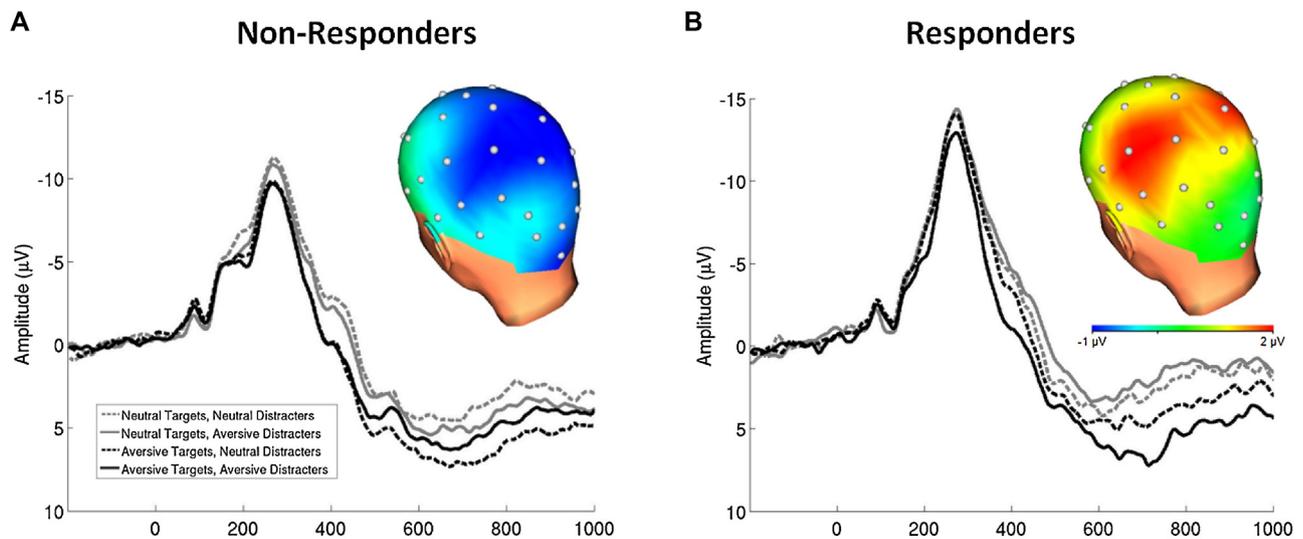

Fig. 2. Grand-average amplitudes for each trial type and spatial distributions of amplitude differences (from 400 to 1000 ms after picture onset) for aversive minus neutral distracters under conditions of aversive targets, shown separately for Non-Responders (CGI-Severity and CGI-Improvement ≥ 3; panel A) and Responders (CGI-Severity and CGI-Improvement <3; panel B).

Responders (Fig. 2b).[1] There was a significant three-way interaction between target type, distracter type, and CGI responder status for the LPP ($F(1,29) = 4.87$, $p = 0.04$, $\eta_p^2 = 0.14$), after controlling for pre-treatment CGI-Severity. Post-hoc tests indicated that when targets were aversive, larger LPPs for aversive (relative to neutral)

distracters were associated with a greater likelihood of recovery (Wald $\chi^2(1) = 4.35$, $p = 0.04$, $OR = 1.44$, $CI = 1.02$-2.03, Nagelkerke $\Delta R^2 = 0.21$) (Fig. 2). None of the other trial-type differences (i.e., aversive minus neutral distracter when targets were neutral; aversive minus neutral target when distracters were neutral/aversive) were associated with recovery status ($ps > 0.13$). Similarly, there was a significant three-way interaction between target type, distracter type, and post-treatment HAM-D ($F(1,29) = 6.23$, $p = 0.02$, $\eta_p^2 = 0.18$), after controlling for pre-treatment HAM-D scores. Larger LPPs for aversive (relative to neutral) distracters when targets were aversive were associated with lower levels of depression at post-treatment ($\beta = -0.36$, $t = -2.28$, $p = 0.03$, $\Delta R^2 = 0.13$)

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[1] Per a reviewer's suggestion, we also examined whether responders and non-responders differed in the N2, an ERP that is thought to represent cognitive control functioning. The N2 was maximal between 250 and 300 ms at Fc1, Fc2, Cz, and Fcz, for which a pooled variable was created for each of the four trial types. Responders and non-responders did not differ on N2 amplitudes as a function of target valence, distracter valence, or their interaction.
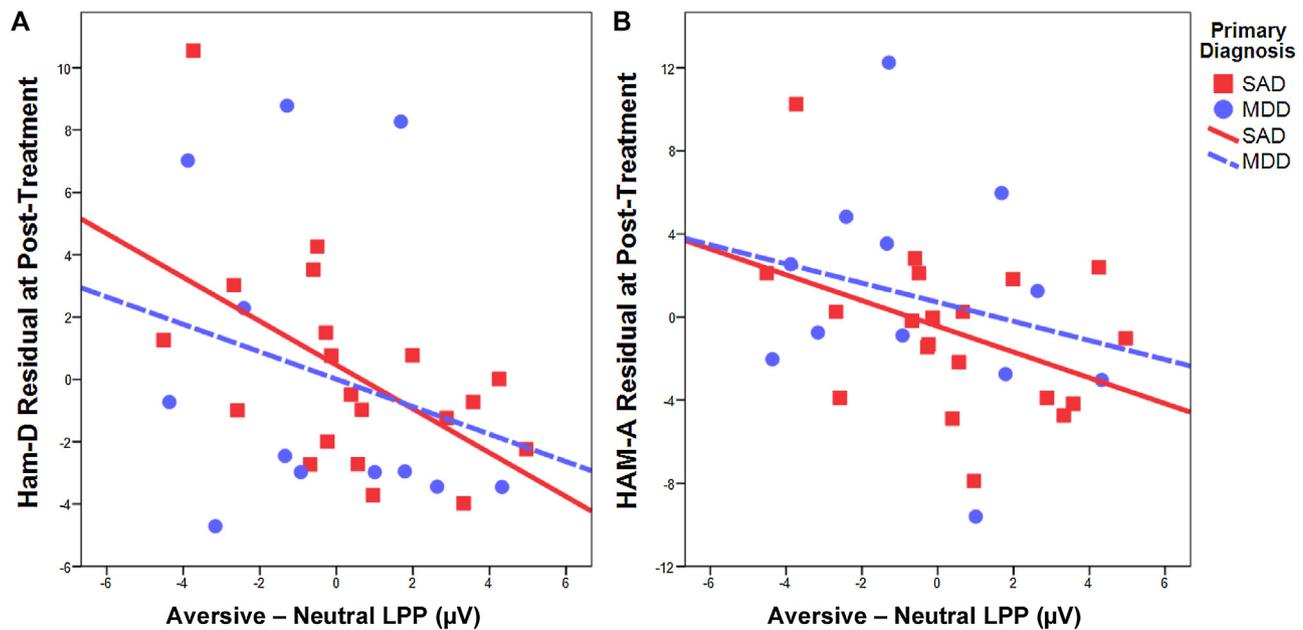
Fig. 3. Scatterplots of associations between pre-treatment LPP (difference between aversive and neutral distracters on aversive target trials) and post-treatment residual Hamilton Depression Rating Scale scores (HAM-D; controlling for pre-treatment HAM-D; panel A) and post-treatment Hamilton Anxiety Rating Scale scores (HAM-A; controlling for pre-treatment HAM-A; panel B), plotted by primary diagnosis (SAD = social anxiety disorder; MDD = major depressive disorder).

(Fig. 3a). None of the other pairwise trial-type differences were associated with post-treatment HAM-D (ps > 0.05).

There also was a significant three-way interaction between target type, distracter type, and post-treatment HAM-A ($F(1,29) = 5.29$, $p = 0.03$, $\eta_p^2 = 0.15$), after controlling for pre-treatment HAM-A. Post-hoc tests indicated that when targets were aversive, larger LPPs for aversive (relative to neutral) distracters were associated at a trend level with lower levels of anxiety symptoms at post-treatment ($\beta = -0.31$, $t = -1.96$, $p = 0.06$, $\Delta R^2 = 0.09$) (Fig. 3b). None of the other three pairwise trial-type differences were associated with post-treatment HAM-A (ps > 0.15).

All treatment prediction results reported above maintained significance when accounting for patients' primary diagnosis (SAD vs. MDD; ANCOVA 3-way interaction terms ps < 0.05). There were no significant interactions between outcome variables and target type, distracter type, or the target x distracter interaction for response time (ps > 0.14) or accuracy (ps > 0.16).

4. Discussion

We evaluated neural markers of attention to aversive stimuli (as indexed by the LPP) as a predictor of response to CBT for SAD or MDD. Results showed that patients with larger LPPs for aversive relative to neutral distracters (when targets were aversive) showed greater response to CBT. These results were evident when using responder status based on CGI ratings, as well as when using continuous changes in depression and anxiety on the HAM-D and HAM-A, respectively. Thus, the LPP at pre-treatment predicted reductions in symptoms evident across a number of clinical measures. These findings support the utility of assessing negative valence systems transdiagnostically using neurobiological measures, to evaluate predictors of treatment outcome in search of a personalized approach to the treatment of anxiety and depressive disorders (Gibb et al., 2015; Sanislow et al., 2010; Simpson, 2012).

In line with prior studies that used fMRI (Doehrmann et al., 2013; Klumpp et al., 2013; Kujawa et al., 2016), we found that greater attention toward aversive stimuli at pre-treatment pre-

dicted superior response to CBT. Although speculative, it is possible that individuals who demonstrate increased attention toward aversive stimuli have a greater tolerance for (or are less avoidant of) aversive emotions, which could facilitate engagement with (or habituation to) these target emotions as part of CBT and therefore could lead to improved treatment response. Alternatively, individuals with greater attention toward aversive stimuli may benefit more from participating in treatments that involve engagement with difficult emotions because these treatments target the reduction of these very characteristics (i.e., one of the aims of CBT is to improve increase tolerance of negative thoughts and emotions). Consistent with this hypothesis, emotional disorders may impair the recruitment of prefrontal regions and filtering of negative, task-irrelevant information (Bishop, Duncan, Brett, & Lawrence, 2004; Bishop, Duncan, & Lawrence, 2004; Bishop, 2009; MacNamara, Ferri, & Hajcak, 2011; Peckham et al., 2010). Thus, larger LPPs to aversive distracters may signal attenuated top-down control of attention to aversive stimuli (Pessoa et al., 2002), suggesting that treatments that aim to improve this top-down control might be a particularly good match for these patients. That treatment outcome was most evident in the presence of negative targets and negative distracters suggests that conditions containing a high load of aversive stimuli (and thus an implicit need for regulation) may be necessary for differentiating which individuals are most likely to benefit from CBT. It also suggests the importance of assessing attention to aversive stimuli using behavioral tasks that contain valenced targets and distracters, as treatment outcome may not have been evidence in the absence of distracters in the task used here.

In contrast with our findings, a related literature has suggested that cognitive flexibility is longitudinally associated with improved symptom course in anxiety and depression (e.g., Johnco, Wuthrich, & Rapee, 2014; Stange et al., 2016). For example, a recent paper demonstrated that superior cognitive flexibility, as indexed by the N2 ERP, was associated with less-distressing intrusive symptoms following an analog trauma (Streb, Mecklinger, Anderson, Johanna, & Michael, 2016). In our study, the behavioral task evaluated

engagement with aversive stimuli in variable locations (targets and distracters) using the LPP, rather than measuring cognitive flexibility per se, which could account for the different pattern of results found here. In addition, naturalistic predictors of symptom course are not necessarily the same as those that may predict response to treatment; for example, cognitive flexibility in general could facilitate reductions in symptom course in naturalistic contexts, but inflexibility with respect to emotional stimuli could represent a target representing greater room for improvement with treatment for emotional disorders. Thus, future research is needed to clarify the contexts in which cognitive flexibility and engagement with emotional stimuli may be associated with symptom course and outcome in naturalistic and treatment contexts.

The study involved a diagnostically-mixed sample of patients receiving treatment for primary SAD or MDD, suggesting that the mechanisms by which larger LPPs to aversive stimuli might be associated with treatment outcome could be at least partially overlapping for these disorders. Larger LPPs to aversive stimuli may indicate less avoidance of these stimuli, which may facilitate habituation in exposure-based treatments (e.g., Jaycox, Foa, & Morral, 1998); individuals with greater avoidance (or smaller LPPs to aversive stimuli) may, on the other hand, be less ready for or less able to benefit from CBT (Tillfors, Furmark, Carlbring, & Andersson, 2015; Waters & Kershaw, 2015). Patients who show a blunted pattern of responding to aversive stimuli (e.g., Proudfit et al., 2015; Bruder, Kayser, & Tenke, 2012) may have difficulty with experiencing and modifying negative emotions in therapy, leading to poorer treatment response. Prior work has documented opposite patterns of LPPs to aversive stimuli among individuals with anxiety and depression in the absence of treatment (e.g., MacNamara et al., 2015; Proudfit et al., 2015). However, the mechanisms discussed here could help to explain why our pattern of results was consistent transdiagnostically and when predicting symptoms of anxiety and depression. Thus, across anxiety and depressive disorders, larger LPPs for aversive relative to neutral stimuli could be an indicator of the ability to engage with difficult emotions (Weinberg & Hajcak, 2011; Proudfit, Dunning, Foti, & Weinberg, 2013), which previously has been shown to facilitate response to CBT (Jaycox et al., 1998; Kashdan, Barrios, Forsyth, & Steger, 2006; Whelton, 2004).

This was the first study to identify the LPP as a predictor of response to CBT among a heterogeneous sample of patients with emotional disorders. Nevertheless, several limitations should be noted. The sample size was relatively small, which prevented us from determining if results differed by primary diagnosis. In addition, the lack of a wait-list control group means that our findings could be predictive of symptom-based change more broadly (e.g., remittance of symptoms due to the passage of time), rather than CBT-based change in particular. Future studies also would benefit from employing multiple treatments and control conditions to determine whether the LPP can be used to identify which patients are most likely to benefit from one treatment versus another, with the goal of personalized medicine (Tracy, Klonsky, & Proudfit, 2014). Although predictors of treatment response are necessarily the same as those that are changed by treatment (e.g., Doehrmann et al., 2013; Klumpp et al., 2013; MacNamara et al., 2015; Phan et al., 2013), examining the degree to which neural responses change following treatment would help to elucidate these questions. It also will be important to evaluate the extent to which findings converge across different tasks and stimulus/distracter types (e.g., idiographic, loss-related stimuli). Relatedly, we did not include a passive viewing task in the present study, so we are not able to specify whether similar results would be found in this context. It is possible that rapidly presented stimuli are more likely to elicit larger LPPs among anxious individuals (e.g., MacNamara & Hajcak, 2009, 2010) than are pictures that are passively viewed

(e.g., Weinberg & Hajcak, 2011); however, future work is needed to determine whether rapidly presented (vs. passively viewed) stimuli might be differentially associated with treatment response. Finally, although post-hoc tests only were conducted when interaction analyses were statistically significant, due to the preliminary nature of this study we did not apply correction for multiple comparisons when testing the simple effects of interactions.

In conclusion, the data provide evidence that patients with larger LPPs to aversive relative to neutral stimuli may be particularly likely to benefit from CBT for anxiety or depression. Results were not observed for behavioral measures, in line with the notion that neural measures may provide particularly sensitive means of assessing elaborative attentional processing of emotional stimuli (e.g., Doehrmann et al., 2013; Kujawa et al., 2016) and underscoring the importance of including such measures in future studies of treatment outcome prediction (Tracy et al., 2014).

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