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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 electroencephalography 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.

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-

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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.