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Suppression of error-preceding brain activity explains exaggerated error monitoring in females with worry

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ABSTRACT

Anxiety is consistently associated with hyperactive neural responses to errors. The majority of existing research has focused on a single marker of error-elicited brain activity—the error-related negativity (ERN), an event-related brain potential (ERP) elicited 50–100 ms following an erroneous response. The ERN has accumulated growing interest for its use in clinical contexts as a potential biomarker and/or endophenotype. However, it is unknown whether anxiety's effects are specific to brain activity following erroneous responses; anxiety may affect processes prior to error commission, suggesting that the ERN might reflect the output of abnormal processing that begins before an error. Here, we examined the error-preceding positivity (EPP) – an ERP time-locked to the correct response immediately before errors – that reflects a gradual disengagement of task-focused attention preceding errors. Results revealed that female worriers demonstrated significantly attenuated EPP amplitude, indicating reduced pre-error disengagement. Moreover, reduced EPP mediated the relationship between worry and the enhanced ERN following errors. These results suggest that the temporal dynamics of anxiety's impact on error processing are more nuanced than previously thought such that effects emerge prior to the actual occurrence of an erroneous response.

1. Introduction

Anxiety and its disorders constitute some of the most common mental health problems in the world and cost billions of dollars each year in treatment and lost work productivity (e.g., Baxter, Scott, & Whiteford, 2013; Baxter, Vos, Scott, Ferrari, & Whiteford, 2010; Kazdin & Blase, 2011; Kessler, Chiu, Demler, & Walters, 2005). Recent years have seen an explosion of research focused on understanding the basic cognitive mechanisms that give rise to and maintain anxiety (e.g., MacLeod & Mathews, 2012; Teachman, Joormann, Steinman, & Gotlib, 2012). In particular, the methods of cognitive neuroscience have been seen as a promising tool for identifying novel markers of pathology and treatment targets (Cuthbert, 2014; First, 2012; Insel et al., 2010; Insel, 2007; Siegle, Ghinassi, & Thase, 2007; Simpson, 2012). The current study took such an approach to elaborate on a key cognitive bias associated with anxiety—exaggerated error monitoring.

1.1. Anxiety and the error-related negativity (ERN)

One of the most consistently reported neurocognitive markers of anxiety and its disorders is increased amplitude of the error-related negativity (ERN), an event-related brain potential (ERP) elicited after errors in simple reaction time tasks (Falkenstein, Hoormann, & Hohnsbein, 1999; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Gehring, Liu, Orr, & Carp, 2012). The ERN occurs immediately (within 100 ms) after response errors and has been reliably associated with regions of the medial frontal cortex such as the anterior cingulate cortex (ACC; Dehaene, Posner, & Tucker, 1994; Gehring et al., 2012; Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter, 2004; van Veen & Carter, 2002). The ACC has been broadly implicated in the neural circuitry associated with monitoring for errors and conflicts in performance (Carter et al., 1998; Kerns et al., 2004; MacDonald, Cohen, Stenger, & Carter, 2000; van Veen & Carter, 2006) and signaling to other brain regions that behavioral adjustment is necessary (MacDonald et al., 2000; Shenhav,

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Botvinick, & Cohen, 2013). As such, the ACC has long been considered necessary for optimal performance and cognitive control (Shackman et al., 2011), and indeed, enhanced ACC activity often coincides with improved performance (e.g., Gehring et al., 1993; Holroyd & Coles, 2002; Yeung, Botvinick, & Cohen, 2004). However, the vast majority of ERN studies of anxiety find enhanced ERN despite no improvements in performance (see Moser, Moran, Schroder, Donnellan, & Yeung, 2013; Weinberg, Riesel, & Hajcak, 2012 for reviews).

The ERN is enhanced among individuals diagnosed with generalized anxiety disorder (e.g., Weinberg, Olvet, & Hajcak, 2010; Xiao et al., 2011), obsessive-compulsive disorder (e.g., Gehring, Himle, & Nisenson, 2000; Klawohn, Riesel, Grützmann, Kathmann, & Endrass, 2014; Riesel, Endrass, Kaufmann, & Kathmann, 2011), as well as individuals with elevated levels of trait worry (e.g., Hajcak, McDonald, & Simons, 2003, Hajcak, McDonald, & Simons, 2004; Moser, Moran, & Jendrusina, 2012) and obsessive-compulsive symptoms (Grundler, Cavanagh, Figueroa, Frank, & Allen, 2009; Hajcak & Simons, 2002; Kaczkurkin, 2013). Developmental studies indicate that enhanced ERN in anxiety is present among children and adolescents (e.g., Hanna et al., 2012; Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006; Torpey et al., 2013).

Given the robust relationship between anxiety and the ERN, understanding its clinical utility as a biomarker of risk for developing an anxiety disorder has become a focus of research (e.g., Manoach & Agam, 2013; Weinberg et al., 2012; Weinberg, Dieterich, & Riesel, 2015). This interest is readily apparent in the number of studies devoted to understanding the heritability (Anokhin, Golosheykin, & Heath, 2008), genetic associations (e.g., Beste et al., 2013; Fallgatter et al., 2004), and basic psychometric properties of the ERN (e.g., Meyer, Riesel, & Proudfit, 2013; Riesel, Weinberg, Endrass, Meyer, & Hajcak, 2013). Indeed, many authors have argued the enlarged ERN may represent an endophenotype for anxiety and anxiety-related disorders (Olvet & Hajcak, 2008; Riesel et al., 2011; Riesel, Endrass, Auerbach, & Kathmann, 2015).

Despite the widespread interest in utilizing the ERN as a biomarker of anxiety, surprisingly few have considered the functional significance of enlarged ERN in anxiety. Early studies suggested the enlarged ERN was the result of a hyperactive response monitoring system (Gehring et al., 2000) whereas others suggested it reflected sensitivity to errors in anxious individuals (Hajcak et al., 2003). In a meta-analysis and theoretical conceptualization (Moser et al., 2013), we have recently incorporated cognitive models of anxiety (attentional control theory, ACT; Eysenck, Derakshan, Santos, & Calvo, 2007) and cognitive control (Braver, 2012; Yeung et al., 2004) to account for increased ERN in anxiety. Our meta-analysis found that the relationship between anxiety and the ERN is specific to the anxious apprehension/worry subtype of anxiety, as opposed to more physiological/unspecified types of anxiety. Our compensatory error-monitoring hypothesis (CEMH) attempted to account for this anxious neurocognitive profile of exaggerated error-monitoring brain activity but equivalent (and not improved) performance. We proposed that enlarged ERN is reflective of a compensatory effort process that worriers engage in to counteract the resource-depleting effects of worries. We hypothesized that the ERN could reflect the output of this process, suggesting that error-monitoring abnormalities associated with anxiety likely begin prior to the error. However, there has been no study examining pre-error brain activity in anxiety, a void the current study sought to fill.

1.2. Brain activity preceding errors

Regardless of the specific cause, most errors are preceded by a gradual decline in task-related attention (Eichele et al., 2008; Eichele, Juvodden, Ullsperger, & Eichele, 2010; Steinhauser et al., 2012). This decline in attention has been captured by functional magnetic resonance imaging (fMRI) studies of the default-mode network (DMN), a collection of brain regions that are classically associated with resting states (Gusnard & Raichle, 2001) and off-task processing (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). As such, past work suggests that errors are preceded by increased DMN activity (Li, Yan, Bergquist, & Sinha, 2007).

ERPs have also been used to capture pre-error brain activity. Earlier research described an ERP that was time-locked to correct responses that precede errors, referred to as the error-preceding positivity (EPP; Allain, Carbonnell, Falkenstein, Burle, & Vidal, 2004; Hajcak, Nieuwenhuis, Ridderinkhof, & Simons, 2005; Ridderinkhof, Nieuwenhuis, & Bashore, 2003). Specifically, this response-locked ERP is larger (i.e., more positive) on pre-error trials versus pre-correct trials. The EPP has been suggested to reflect the gradual attentional decline immediately preceding errors (Hajcak et al., 2005; Li et al., 2007; Simons, 2010) and has been hypothesized to reflect DMN activity (Li et al., 2007). Unfortunately, few studies have examined the EPP, and despite the plethora of anxiety-ERN papers described above, no study has examined the relationship between anxiety and the EPP (or how anxiety relates to pre-error brain activity using fMRI). Thus, our knowledge about how anxiety influences error monitoring is constrained to brain activity that occurs after errors are committed.

This study sought to address this gap in knowledge by examining how anxiety impacts error processing before errors are committed. Investigating the relationship between anxiety and pre-error brain activity (i.e., the EPP) would be informative for several reasons. First, it would provide for a more comprehensive understanding of how anxiety influences error monitoring by extending the temporal focus to trials leading up to the error. Indeed, the neural activity associated with the ERN does not occur in isolation; rather, it is part of a system involved in monitoring performance that likely waxes and wanes in activity during trials surrounding errors (Ridderinkhof et al., 2003; Steinhauser et al., 2012). Extending the window of focus would also allow us to test our hypothesis that error-monitoring modulations (compensatory effort) associated with anxiety are present before the error occurs (Moser et al., 2013). Second, from a clinical standpoint, the EPP may provide incremental understanding of the etiology and risk for anxiety, in addition to the ERN. Third, because it is captured on trials immediately before errors, the EPP can be extracted from any ERN dataset, regardless of paradigm (cf. Hajcak et al., 2005; Masaki, Murphy, Kamijo, Yamazaki, & Sommer, 2012), allowing for the re-analysis of existing datasets and therefore an amassing of a corpus of novel information related to anxiety and error processing.

Finally, although no study has examined error-preceding brain activity and anxiety specifically, extant neuroimaging research strongly suggests such a link might exist. Specifically, an increasing number of studies show DMN abnormalities in anxiety (Andreescu, Sheu, Tudorascu, Walker, & Aizenstein, 2013; Anteraper et al., 2014; Bijsterbosch, Smith, Forster, John, & Bishop, 2014; Fales et al., 2008; Gentili et al., 2009; Liu et al., 2014; Zhao et al., 2007; see Sylvester et al., 2012 for a review). Although most of these studies examined how anxiety relates to DMN activation during resting states, Fales et al. (2008) found that trait anxiety was associated with a sustained (task-wide) *de*activation of DMN regions during a cognitive control task. Fales et al. suggested that sustained DMN deactivation reflected greater compensatory effort among individuals with anxiety to either enhance performance or to suppress distracting anxiety-related thoughts when task attention began to decline. That is, the suppression of DMN activity was thought to be compensatory. Such an interpretation is entirely consistent with our model (Moser et al., 2013, 2014). Moreover, the regions identified in the Fales et al. study – including posterior cingulate cortex, precuneus, perigenual ACC, and frontopolar cortex – overlap with those impli-