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Blunted neural response to errors as a trait marker of melancholic depression

Anna Weinberg[1], Huiting Liu, Stewart A. Shankman*

University of Illinois at Chicago, United States

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ABSTRACT

Identification of biomarkers of vulnerability for Major Depressive Disorder is a high priority, but heterogeneity of the diagnosis can hinder research. Biomarkers of vulnerability should also be present in the absence of the diagnosis. The present study examined the magnitude of the error-related negativity (ERN), an event-related potential component following errors in a sample with remitted melancholic depression ($N = 17$), remitted non-melancholic depression ($N = 33$), and healthy controls ($N = 55$). Remitted melancholic depression was uniquely characterized by a blunted ERN relative to the other two groups. Individuals with remitted non-melancholic depression did not differ from controls in the magnitude of the ERN. This was the case despite the fact that the melancholic and non-melancholic groups did not differ in course or severity of their past illnesses, or in their current functioning. Results suggest that the blunted ERN may be a viable vulnerability marker for melancholia.

1. Introduction

Major Depressive Disorder (MDD) is one of the most common and costly forms of illness worldwide (Greenberg, Stiglin, Finkelstein, & Berndt, 1993; Mathers, Fat, & Boerma, 2008; Murray et al., 2013). Yet, despite its prevalence and considerable public health impact, the pathophysiology of depression is not well understood (Krishnan & Nestler, 2008). Efforts to identify reliable and stable biomarkers of vulnerability for the disorder have often been inconclusive due, in part, to the heterogeneity of diagnostic categories (Cuthbert, 2014; Cuthbert & Insel, 2013; Helzer, Kraemer, & Krueger, 2006; Klein, 2008). Different symptoms and symptom clusters subsumed under the MDD diagnosis appear to have distinct etiologies (Day et al., 2015), clinical features (Kendler, 1997), courses (Angst, Gamma, Benazzi, Ajdacic, & Rössler, 2007; Lux & Kendler, 2010), and biological correlates (Pizzagalli et al., 2004), which are likely obscured in studies that only compare those with MDD to controls. Examining more specific processes and symptom clusters may help bridge biological and psychological data and identify vulnerability markers (Insel et al., 2010; Shankman & Gorka, 2015).

Neural response to errors appears to be a viable neurobiological marker of psychopathology (Manoach & Agam, 2013; Vaidyanathan, Nelson, & Patrick, 2012; Weinberg, Dieterich, & Riesel, 2015). In particular, the error-related negativity (ERN; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993), an event-related potential (ERP) response to errors, may be useful in research concerned with the pathophysiology of depression (Weinberg, Dieterich et al., 2015). The ERN appears as a negative-going deflection in the ERP waveform at frontocentral sites, between 0 and 100 ms following the commission of an error. There are multiple functional explanations for the ERN, the majority of which agree that the ERN reflects an alarm signal following error commission—a call to increase cognitive control and adjust behavior (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Gehring et al., 1993; Holroyd & Coles, 2002; Holroyd & Yeung, 2012).

Multiple lines of research strongly implicate the ACC, a part of the frontostriatal system, as the neural generator of the ERN (Brázdil, Roman, Daniel, & Rektor, 2005; Debener et al., 2005; Ito, Stuphorn, Brown, & Schall, 2003; Miltner et al., 2003; Reinhart & Woodman, 2014; Stemmer, Segalowitz, Witzke, & Schönle, 2004). However, the ACC is richly innervated by dopaminergic neurons (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001), and neurotransmission of dopamine (DA), which mediates stimulus salience as well as motoric control, influences the magnitude of the ERN. For instance, DA agonists enhance the ERN (De Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004), while DA antagonists attenuate it (De Bruijn

* Corresponding author at: Department of Psychology, University of Illinois at Chicago, Chicago, IL 60607, United States.
E-mail address: stewarts@uic.edu (S.A. Shankman).
[1] Present address: Department of Psychology, McGill University, Stewart Biology Building, 1205 Dr. Penfield Avenue, Montreal, Quebec H3A 1B1, Canada.

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et al., 2004; Zirnheld et al., 2004). Similarly, neuropsychological diseases in which dysfunction of the mesencephalic DA system plays a central role, like Parkinson's (Falkenstein, Willemssen, Hohnsbein, & Hielscher, 2006) and Huntington's disease (Beste, Saft, Andrich, Gold, & Falkenstein, 2006) have been associated with attenuated ERN amplitudes. Genetic polymorphisms governing DA neurotransmission can also influence error processing in both healthy and neuropsychiatric populations (Manoach & Agam, 2013). Moreover, there is evidence that the magnitude of the ERN depends in part on efference motor signals from the cerebellum, routed through the thalamus, that adaptively adjust basal ganglia activity on the basis of a perceived mismatch between desired and actual response (i.e., an error) and adjust behaviors accordingly (e.g., Peterburs et al., 2011, 2012, 2015; Seifert, von Cramon, Imperati, Tittgemeyer, & Ullsperger, 2011). Studies of patients with either cerebellar or thalamic lesions, for instance, have demonstrated that disturbed communication between the basal ganglia, cerebellum, and thalamus and the frontal cortex is reflected in a blunted ERN (Peterburs et al., 2011, 2012).

Abnormalities in the magnitude of the ERN have been identified in diverse forms of psychopathology, including depression (Weinberg, Dieterich et al., 2015). However, the literature on the ERN in depression is far from consistent. For instance, though several studies have demonstrated that a diagnosis of depression is associated with a blunted ERN (Ladouceur et al., 2012; Schoenberg, 2014; Schrijvers et al., 2008; Weinberg, Meyer et al., 2015), others have demonstrated an enhanced ERN in depression (Aarts, Vanderhasselt, Otte, Baeken, & Pourtois, 2013; Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008a; Holmes & Pizzagalli, 2010; Tang et al., 2013). Still others have found no evidence of difference from controls (Olvet, Klein, & Hajcak, 2010; Ruchsow et al., 2006; Schrijvers et al., 2009; Weinberg, Klein, & Hajcak, 2012; Weinberg, Kotov, & Proudfit, 2015). One possibility underlying these mixed results is that the aforementioned diagnostic heterogeneity within MDD is obscuring meaningful variation in neural response. For instance, even within depressed groups, there is evidence that symptom profiles associated with reduced DA functioning and motoric disturbances, particularly psychomotor retardation, uniquely predict a reduced ERN (Schrijvers et al., 2008; Weinberg, Kotov et al., 2015). Other studies in depressed populations have also found that more severe symptoms of anhedonia predicted a more blunted ERN (Olvet et al., 2010).

Depression in general has often been associated with reduced DA transmission (Dunlop & Nemeroff, 2007). Yet this impairment may be most pronounced in melancholic depression (Baumeister & Parker, 2012; Parker, 2007; Parker et al., 1995), a specifier within the MDD category which has long been thought to have a more neurobiological etiology than other depressive subtypes (Baumeister & Parker, 2012; Fava et al., 1997; Klein, 1974; Pizzagalli et al., 2004). Indeed, the cardinal symptoms of melancholia are pervasive anhedonia and psychomotor disturbances, in particular psychomotor retardation, which typically manifests as slowing across one or more of the following domains: facial movements, gait, speech and thought processes (Parker, 2007; Parker et al., 1995). This neurocognitive retardation also may persist at a discernable level even after recovery from depression, and relate to the severity of depression (e.g., Gorwood, Richard-Devantoy, Baylé, & Cléry-Melun, 2014). Given the association between DA functioning, motoric disturbances, and the ERN, and evidence that melancholic depression might be more strongly characterized by DA dysfunction and motor disturbances than other depressive subtypes, the present study sought to examine the ERN in individuals who met criteria for melancholic and non-melancholic forms of depression.

In addition to examining the effect of diagnostic heterogeneity, we were interested in whether the ERN might represent a viable *vulnerability* marker for some depressive phenotypes but not others. Research on the psychometric properties of the ERN suggest that it is relatively trait-like, in that it is a stable (Foti, Kotov, & Hajcak, 2013; Meyer, Riesel, & Proudfit, 2013; Olvet & Hajcak, 2009c) and reliable neural signal (Olvet & Hajcak, 2009b; Segalowitz et al., 2010; Weinberg & Hajcak, 2011) with excellent internal consistency (Riesel, Weinberg, Endrass, Meyer, & Hajcak, 2013). Additionally, there is evidence that the magnitude of the ERN is subject to substantial genetic influence (Anokhin, Golosheykin, & Heath, 2008), and abnormalities in the ERN have been observed in unaffected family members of individuals with psychopathology (Carrasco et al., 2013; Euser, Evans, Greaves-Lord, Huizink, & Franken, 2013; Riesel, Endrass, Kaufmann, & Kathmann, 2011; Torpey et al., 2013), as well as other high-risk populations (Lahat et al., 2014; Meyer et al., 2014). Combined, these data suggest the ERN is a viable candidate for a heritable, trait-like risk marker (Manoach & Agam, 2013; Vaidyanathan et al., 2012; Weinberg, Riesel, & Hajcak, 2012).

If the ERN does represent a stable vulnerability factor, abnormalities in the magnitude of the ERN should also be primarily state-independent, and not linked to changes in symptom severity. Thus, if a blunted ERN is a potential trait marker of melancholic depression, it should also be evident in those with remitted melancholic depression. To date, three studies have examined the ERN in remitted MDD, and have found mixed results (Alexopoulos et al., 2007; Georgiadi, Liotti, Nixon, & Liddle, 2011; Schoenberg, 2014). One of these found that individuals with current MDD exhibited a blunted ERN relative to controls, but those with remitted MDD did not (Schoenberg, 2014). Another found a reduced ERN in a group who had remitted from depression relative to those who did not remit (Alexopoulos et al., 2007). The third found that remitted MDD was characterized by an *enhanced* ERN relative to controls, but that current MDD did not differ from controls (Georgiadi et al., 2011). Yet each of these studies only examined MDD as a single category, suggesting again that diagnostic heterogeneity within the depressive category can hinder research on biomarkers for depression.

The present study therefore had two goals: the first was to examine whether inconsistencies regarding the ERN in depression could be resolved by studying the subtype of melancholic depression. The second was to examine whether the ERN might represent a state-independent vulnerability marker. To meet these goals, we examined the magnitude of the ERN in a sample of individuals with remitted MDD (melancholic type), remitted MDD (non-melancholic type), and healthy controls (HC). We predicted that the magnitude of the ERN would be blunted in remitted melancholic depression relative to both controls and remitted non-melancholic depression. In order to explore whether the magnitude of the ERN related more to current functioning, or might instead represent a vulnerability marker, we also examined current symptoms and functioning between the two remitted depressed groups.

2. Method

2.1. Participants

The participants in the current sample were selected from a larger sample of siblings, recruited to have a broad spectrum of psychopathology. In the analyses described below, only one sibling per pair was included (see Weinberg, Liu, Hajcak, & Shankman, 2015, for details on the larger sample). Participants were recruited from the community and area mental health clinics (via fliers, Internet postings, etc.), on the basis of symptoms of anxiety and depression, and were screened via telephone using the Depression, Anxiety, and Stress Scale (DASS; Lovibond & Lovibond, 1995). Because manic and psychotic symptoms have been shown to be separable from internalizing disorders (Watson, 2005), participants were excluded