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COMMENTARY

The error-related negativity: A transdiagnostic marker of sustained threat?

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Abstract

The creation of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project has been the driving force behind the reconceptualization of the pathogenesis of psychiatric disorders. In this commentary, I explore whether the error-related negativity can be considered as a transdiagnostic marker of sustained threat based on findings from Weinberg, Meyer et al.'s (2016) study in relation to current findings in the literature. Potential alternative study designs, use of a multimodal approach to the assessment of a specific phenotype of clinical phenomenon, and the importance of integrating a neurodevelopmental perspective are also discussed.

Descriptors: Error-related negativity, RDoC, Transdiagnostic marker, Neurodevelopment

The recent advent of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project has prompted investigators to think differently about how to design scientific studies aimed at understanding the pathophysiology of psychiatric disorders. Traditionally, studies have been designed to compare a clinical sample to a group of well-matched healthy participants on various behavioral or neurobiological measures. As described in **Kozak and Cuthbert's (2016)** paper, conclusions from such studies have yielded very little information regarding the way in which alterations in emotional, cognitive, or behavioral functioning could be contributing to the clinically observed impairments. The RDoC framework was created to foster translational research by proposing a set of psychological constructs that can be determined dimensionally and for which there is compelling evidence that there are underlying neural circuits subserving these functions. Using such an approach could enhance our ability to discover how particular types of alterations in the structure or functioning of neural circuitries map on to extreme functioning in specific psychological constructs (e.g., visual or auditory perception of threat cues) in ways that can explain specific psychiatric symptoms. Ultimately, the goal of this initiative is to potentially discover mechanisms underlying specific types of impairments or clinical phenomena. Such a discovery would set the stage for the development of novel treatment approaches that could target these mechanisms using neuropharmacological, neural stimulation, cognitive and behavioral modification, or a combination of these approaches. Moreover, understanding the developmental mechanisms underlying neuromaturational changes that contribute to alterations in specific neural circuitries as well as identifying developmental windows of heightened neuroplasticity will be critical to bolstering the effectiveness of such intervention strategies (Cramer et al., 2011).

The error-related negativity (ERN), a fast-occurring (approximately 50 ms) frontocentrally maximal negative ERP, represents the brain's automatic detection of an error. Over the past two decades, a growing number of studies have documented more- or less-negative ERN amplitude across various psychiatric disorders such as anxiety disorders (Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006; Weinberg & Hajcak, 2010; Weinberg, Kotov, & Proudfit, 2015), depression (Holmes & Pizzagalli, 2008; Ladouceur et al., 2012; Weinberg, Klein, & Hajcak, 2012), obsessive-compulsive disorder (OCD; Carrasco et al., 2013; Endrass & Ullsperger, 2014; Gehring, Himle, & Nisenson, 2000; Hajcak, Franklin, Foa, & Simons, 2008), schizophrenia (Alain, McNeely, He, Christensen, & West, 2002; Mathalon et al., 2002), addiction (Marhe & Franken, 2014), and attention deficit hyperactivity disorder (ADHD; Herrmann et al., 2010; Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005; Wiersema, Van Der Meere, & Roeyers, 2009). More- or less-negative ERN amplitude represents a dimensional measure of activity of a population of neurons that fire in synchrony and implicate a neural network that is centered on the anterior cingulate cortex (ACC) and includes prefrontal cortical and subcortical limbic regions (Stevens, Kiehl, Pearlson, & Calhoun, 2009). Several neural models have been proposed to explain the functional role of the ERN (Gehring, Coles, Meyer, & Donchin, 1995; Hajcak, Moser, Yeung, & Simons, 2005; Holroyd & Coles, 2002; Luu & Tucker, 2004; Yeung, Botvinick, & Cohen, 2004). Some of these models focus more on the cognitive subprocesses implicated in error processing (Yeung et al., 2004) while others focus more on the implications of making an error for

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learning (Holroyd & Coles, 2002) and adaptive behavior (Hajcak et al., 2005). Hajcak and colleagues have conceptualized errors as motivationally salient events due to their role in signaling threat to safety (Hajcak, 2012). To test their model, they used variable ERN amplitude as an index of the extent to which errors were experienced as threatening (Hajcak, McDonald, & Simons, 2004; Hajcak et al., 2005; Riesel, Weinberg, Endrass, Kathmann, & Hajcak, 2012; Riesel, Weinberg, Moran, & Hajcak, 2013). In this most recent study, **Weinberg, Meyer et al. (2016)** proposed that the ERN represents a physiological measure of sensitivity to "endogenous threat," which is subsumed under the "sustained threat" construct within the negative valence system of the RDoC matrix (**Weinberg, Meyer et al., 2016**). Do findings from this study, in relation to evidence from other studies in the literature, pass the "litmus test" regarding the placement of the ERN in the sustained threat construct?

If we refer to the RDoC matrix, *sustained threat construct* is defined as "an aversive emotional state caused by prolonged (i.e., weeks to months) exposure to internal and/or external condition(s), state(s), or stimuli that are adaptive to escape or avoid. The exposure may be actual or anticipated; the changes in affect, cognition, physiology, and behavior caused by sustained threat persist in the absence of the threat, and can be differentiated from those changes evoked by acute threat." Using a large sample of typically developing girls ($n = 515$, 13.5–15.5 years old), **Weinberg, Meyer et al. (2016)** show that more-negative ERN amplitude is associated with greater levels of self-reported checking behaviors (i.e., the extent to which people monitor their own behavior in view of reducing the anxiety about potential threat), whereas less-negative ERN amplitudes are associated with depressive symptoms. Checking behaviors represent compulsive behaviors that are typically included as part of the symptoms of OCD, but some studies have reported the presence of checking in other psychiatric conditions (e.g., generalized anxiety disorder, major depressive disorder; Weinberg, Kotov, & Proudfit, 2015). Some have conceptualized checking in terms of avoidance (Aguayo, Melero, & Lázaro, 2014). Indeed, there is abundant evidence showing that repetitive behavior found in OCD receives negative reinforcement when the anxiety generated by the obsession diminishes. If individuals do perceive errors as "threatening" or "catastrophic" and if ERN amplitude "reflects variability in the sensitivity to errors," as suggested by **Weinberg, Meyer et al. (2016)**, then it logically follows that individuals with more-negative ERN amplitude should be more likely to avoid potential threats such as making errors. One could also predict that greater avoidance would be related to more checking behavior. Future work could test this hypothesis by developing a paradigm that would give participants the opportunity to (a) avoid making errors or avoid being punished for making errors, and/or (b) check the number of errors committed to avoid an aversive outcome based on the number of errors. Given that avoidance behavior is placed with the sustained threat construct, relating error-related brain activity to avoidance behavior would strengthen the tenet that the ERN represents a unit of analysis of sustained threat.

Conceptualizing the ERN as an indicator of sustained threat that is related to checking behaviors goes beyond the notion that more-negative ERN amplitude is the result of ACC hyperactivity that could be part of the pathophysiology of trait anxiety or anxiety disorders (Hajcak, McDonald, & Simons, 2003; Ladouceur et al., 2006). Findings from **Weinberg, Meyer et al. (2016)** suggest that more-negative ERN amplitude could index alterations in the functioning of a neural network subserving error processing. Alterations at a network level would thus implicate alterations in specific cognitive (i.e., high levels of monitoring), emotional (i.e., anticipation of highly aversive outcome), and motivational (i.e., negative reinforcement from the reduction of the aversive experience linked with anxiety) processes related to checking. However, without measures of checking behaviors that complement self-report measures used in the Weinberg, Meyer et al. study (e.g., ecological assessment of checking behavior frequency or physiological measures of arousal during or following checking behavior), it is difficult to determine which aspect of checking behavior is particularly linked to ERN amplitudes. Employing a multimodal approach to the assessment of a specific phenotype or clinical phenomena (i.e., subjective, observational, behavioral, physiological) such as checking is essential to the discovery of transdiagnostic biomarkers.

Another point to consider in determining the extent to which the ERN maps onto sustained threat is that the sample consisted of typically developing adolescent girls. Epidemiological studies show that girls are more likely to report symptoms of anxiety and depression than boys this age (Angst et al., 2002). In order to consider ERN amplitude as a useful tracker of levels of checking and depression at a transdiagnostic level, it would be important to replicate this study in a sample of adolescent boys. Boys this age are more likely to exhibit higher levels of risk-taking and impulsive behavior (Steinberg, 2007). Given evidence that less-negative ERN amplitude has been linked with higher risk-taking behavior (Santesso & Segalowitz, 2009), it would follow, according to the motivational salience model (Hajcak, 2012), that greater risk taking would be mediated by a lack of concern or reduced threat valuation regarding errors. If this is the case, is it possible that how much adolescents "care" about the positive or negative outcomes of their own actions represents a latent factor underlying less-negative ERN amplitude in both depression and risk taking? Future studies could address this question by assessing the ERN in the context of risk taking while manipulating levels of reward and punishment contingent upon errors in adolescent girls and boys, and examine how such findings relate to specific phenotypes of anxiety, depression, and risk taking. The extent to which such a latent factor would apply to other types of psychopathology for which less-negative ERN amplitudes have been reported (e.g., schizophrenia, addiction) would also need to be determined. A recent study showed that cocaine addicts who exhibited less-negative ERN amplitude were more likely to relapse within 3 months following treatment compared to those who exhibited more-negative ERN amplitude (Marhe & Franken, 2014). These findings were interpreted as representing a "biomarker for cocaine relapse" (Marhe & Franken, 2014). Some have interpreted this effect in terms of decreased sensitivity to errors in cocaine-dependent individuals associated with reduced activation in the ACC (Franken, van Strien, Franzek, & van de Wetering, 2007; Kaufman, Ross, Stein, & Garavan, 2003). Manipulating the threat value of errors with these various populations could also provide insight into the nature of ERN amplitude variation as it relates to sustained threat.

Another important finding from the **Weinberg, Meyer et al. (2016)** study was that age moderated the association between ERN and checking in that more-negative ERN was associated with checking in older girls. However, there was no moderation effects reported for depression symptoms. Although the age range in this sample was rather narrow (13.5–15.5 years), it covered the developmental window during which adolescents undergo important neurodevelopmental changes related to behavior (Luna, 2009). These findings are also consistent with findings from a recent longitudinal study in 9- to 25-year-olds showing that executive control and error-processing regions mature later than motor response control regions and that error processing neural activation is closely

related to developmental improvements in performance on inhibitory control tasks (Ordaz, Foran, Velanova, & Luna, 2013). Ordaz et al. (2013) also reported sex differences in the trajectories of recruitment of motor control regions, which could help explain why the association between ERN amplitude and checking was stronger for older adolescent girls. In what way could developmental effects (i.e., sex, age, pubertal status) contribute to elucidating potential transdiagnostic phenomena? Although **Kozak and Cuthbert (2016)** do not address the role of developmental research in the development of the RDoC matrix, as discussed in Casey, Oliveri, and Insel (2014), there are several advantages to integrating neurodevelopmental concepts with RDoC principles in order to address clinically relevant questions about the emergence of psychopathology (Casey et al., 2014). Casey et al. put forward three aspects of neurodevelopmental research that would merit integration within the RDoC project: developmental trajectory, sensitive period, and dynamic interaction of systems. Such integration will be important to advance the field with regard to identifying biomarkers of risk, understanding etiology of disorders, and elucidating sensitive periods of targeted intervention strategies that would be grounded in developmental research.

In sum, research focusing on error-related brain activity is a promising avenue toward identifying potential biomarkers that could explain clinically relevant phenomena. **Weinberg, Meyer et al. (2016)** provide compelling data in a large sample of adolescent girls. These findings contribute to setting the stage for future neurodevelopmental research that could further inform the RDoC project. However, research in this area would be enhanced by taking a multimodal and interdisciplinary approach that includes more advanced analytical tools. For example, a recent study using machine learning methods revealed that different kinds of errors show a type of deflection in the EEG with different latency as well as a different spectral response. These methods were used to discriminate between execution and outcome errors (Spüler & Niethammer, 2015). Examining variation in multiple aspects of error-related brain activity (e.g., amplitude, frequency domain) in combination with machine learning methods and multimodal assessments (i.e., observation, behavior, subjective report, etc.) of a particular clinical phenomenon across development (e.g., checking) would help determine the extent to which the ERN represents a transdiagnostic marker of sustained threat.

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