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Mood Disorders (S Frangou, Section Editor)

Developing Psychiatric Biomarkers: a Review Focusing on the Error-Related Negativity as a Biomarker for Anxiety

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Opinion statement

Efforts to identify psychiatric biomarkers that confer clinical utility have not yet been as successful as other areas of medicine. The current review evaluates one promising psychiatric biomarker (the error-related negativity (ERN)—a neural index of error processing) in an attempt to outline a roadmap for the development of future biological markers of risk for psychopathology. Integrating suggestions from the Biomarkers Definition Working Group into a framework of psychopathology, with an emphasis on a developmental perspective, we demonstrate that the ERN relates to diagnoses and dimensional anxiety symptoms concurrently—and can predict new onset disorders prospectively. The ERN appears related to a clinically relevant transdiagnostic phenotype (i.e., the tendency to engage in checking behaviors)—and also differentiates anxiety from highly comorbid conditions such as depression. We emphasize the importance of evaluating the psychometric properties of psychiatric biomarkers, in adults and children, pointing out that the ERN displays excellent internal and test-retest reliability across development. Furthermore, we discuss the diagnostic utility of the ERN as well as animal models of error processing that may pave the way for the development of pharmacological interventions. Finally, we raise the possibility that a psychiatric biomarker can serve as a *target* of treatment, thereby encouraging the development of novel intervention strategies. In the case of the ERN, we discuss the use of attentional training, parenting interventions, and neurostimulation as potential avenues of intervention to alleviate or prevent the onset of anxiety disorders.

Introduction

Medical research has made considerable progress through the use of biomarkers that link measureable biological characteristics to disease states. The examples of such markers include measuring blood pressure to estimate cardiovascular risk, as well as the presence of specific genes—for instance, the relation of *BRCA* genes to breast cancer [1]. As defined by the Biomarkers Definition Working Group [2], a biomarker is "a characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." There has been a substantial push in recent years to identify biomarkers in relation to *psychiatric* illnesses, with some success in this area [3, 4•, 5]. However, efforts to identify psychiatric biomarkers that confer clinical utility have been less successful compared to other areas of medicine [6]. Given that psychopathology often begins early in life, there is a substantial gap in identifying psychiatric biomarkers in a developmental context [7•]. The current review evaluates one promising psychiatric biomarker in an attempt to outline a roadmap for the identification of future biological markers of risk for psychopathology across development.

Overview—the error-related negativity

The current review focuses on the neural response to errors measured by an event-related potential (ERP) called the error-related negativity (ERN). ERPs are summations of voltage fluctuations recorded at the scalp, time-locked to specific events (e.g., stimuli, responses, etc.), and are thought to measure postsynaptic potentials arising when thousands of similarly oriented neurons bind with neurotransmitters in a coordinated fashion [8]. When people make mistakes on simple laboratory-based reaction time tasks, there is a burst of electrical activity that appears as a sharp negative-going peak in the ERP waveform at fronto-central cites (see Fig. 1). This neural response to making mistakes is called the ERN and is thought to reflect a general error detection system in the brain. The ERN is thought to be generated in the anterior cingulate cortex (ACC), a region of the brain where information about pain, threat, and punishment is integrated to change behavior [9]. We have conceptualized errors as a specific type of threat; indeed, errors do prompt a cascade of physiological responses consistent with defensive responding (e.g., skin conductance response, heart rate deceleration, potentiated startle reflex, pupil dilation, corrugator muscle contraction). Given this, we view variability in the neural response to errors as reflecting individual differences in reactivity to an *internal* source of threat. Thus, the ERN has been proposed as a potential biomarker for psychiatric disorders that may be characterized by sensitivity to threat (e.g., anxiety disorders).

The ERN and anxiety

One of the primary properties of a useful psychiatric biomarker is that it measures a normal biological process that is altered in individuals with psychopathology. Beginning with the first study demonstrating that individuals with obsessive-compulsive disorder (OCD) are characterized by an increased ERN [10], the ERN has since been shown to be elevated in anxious individuals

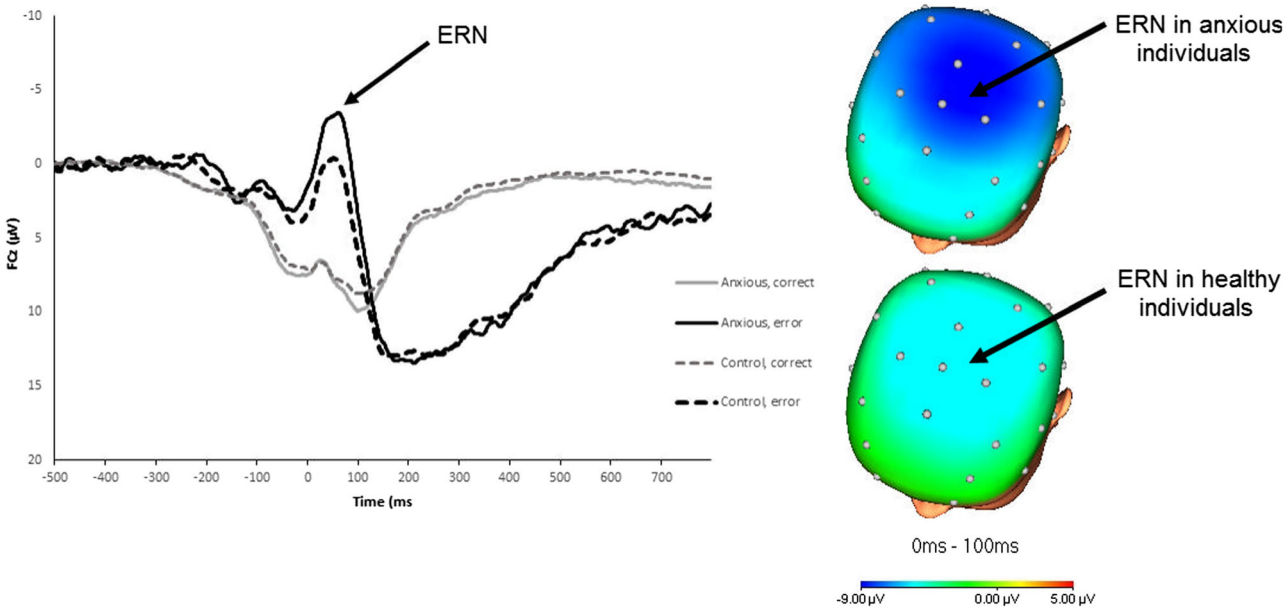

Fig. 1. On the *left*, waveforms at electrode FCz for anxious and non-anxious individuals. As can be seen, from 0 to 100 ms after the response was made, anxious individuals displayed an increased ERN (*dark black line*) compared to healthy controls (*dotted black line*). On the *right*, topographic headmaps depict error minus correct neural activity from 0 to 100 ms after the response. *Darker blue* indicates a larger ERN. Anxious individuals (*top*) were characterized by a more negative ERN than healthy controls (*bottom*).

in over 40 studies to date (for a meta-analysis, see: [11]). We, and others, have replicated this pattern in individuals with OCD [12], generalized anxiety disorder (GAD; [13]), and social anxiety disorder (SAD; [14]). For demonstration purposes, we have included a figure depicting the ERN in anxious ($N = 41$) and non-anxious individuals ($N = 53$) (Fig. 1; data combined from two previous studies). As can be seen in the waveforms and topographic headmaps, individuals with anxiety disorders displayed increased error-related neural activity. Moreover, young children (6 years old) with anxiety disorders are also characterized by a potentiated ERN [15]—suggesting that this biomarker may be useful in tracking developmental trajectories of psychopathology. Furthermore, even when anxiety is not conceptualized in a dichotomous disorder-based fashion, increased anxiety symptoms are related to a potentiated ERN [11]. In light of these findings, the ERN appears to consistently differentiate healthy versus anxious individuals, as well as track anxiety symptoms dimensionally.

Specificity of the ERN

Considering the problem of comorbidity among psychological disorders, the identification of biomarkers that can aid in delineating more specific, and mechanistically defined, manifestations of pathology would be of benefit to the field. Although anxiety and depression are among the most frequently comorbid psychological disorders (e.g., 65 % of individuals with GAD report a lifetime history of depression; [16]), there is evidence that the ERN can differentiate these groups. For example, we found that among a sample of individuals with GAD, individuals with comorbid GAD and MDD and controls,

only the GAD group was characterized by a larger ERN [17]. The ERN was comparable between healthy controls and individuals with comorbid GAD and MDD, suggesting that depression may blunt the tendency for an enhanced ERN in this group. Similarly, we found that anxiety symptoms were uniquely related to the ERN [18•] and then replicated this finding in a large sample of adolescents, finding that anxiety and depression symptoms were related to the ERN in opposing directions, such that depressive symptoms were linked to a smaller ERN and anxiety symptoms were linked to a larger ERN [19•]. This is consistent with other work that has found a blunted ERN in clinically depressed children [20], as well as in children at risk for depression (i.e., children with a maternal history of chornic depression; [21]). Taken together, these studies suggest that the ERN may be a viable biomarker that can differentiate anxiety from depression.

Building on these findings, we have also begun defining more specific anxiety phenotypes that relate to an enhanced ERN. For example, an enhanced ERN is not evident in all anxiety disorders—adults with PTSD and simple phobias are characterized by ERNs that are similar to healthy controls [22, 23]. Indeed, some work suggests that the ERN may relate to a transdiagnostic phenotype characterized by anxious apprehension (i.e., cognitive symptoms of anxiety) as opposed to one characterized by anxious arousal (i.e., acute fear response) [11, 24]. We have recently extended these findings to explore what specific facets of anxious apprehension an enhanced ERN may index—a finding that the ERN uniquely relates to self-reported checking behavior, even when controlling for all other anxiety symptom domains [12, 19•]. Checking reflects the tendency to engage in *self-monitoring of one's own behavior* to reduce anxiety (e.g., repeatedly checking to make sure one turned the coffee pot off or to make sure one locked the door). In light of these findings, it appears that the ERN is not only specific to anxiety versus depression, but can also be tied to a well-defined transdiagnostic construct with behavioral and clinical significance (i.e., checking).

Psychometric properties of the ERN

An often neglected, but necessary property, of a biomarker that indexes individual differences in psychopathology is that it is psychometrically reliable. The validity of an individual difference measure is limited by its reliability [25], such that a measure cannot relate to another variable of interest more than it relates to itself (i.e., its internal reliability). Moreover, internal consistency limits between-subject effect sizes [26]. Fortunately, the ERN has demonstrated excellent psychometric properties—both internally [27] and across testing sessions [28]. We have compared the psychometric properties of the ERN elicited during different tasks and as a function of the number of trials included [29]—identifying an optimal task (i.e., the flankers task) and minimum number of errors required (i.e., 6–10). In light of the fact that psychopathology often emerges early in development, it is important to validate psychiatric biomarkers in children and adolescents. We have examined the psychometric properties of the ERN in a developmental population—finding excellent internal and test-retest reliability for up

to 2 years [30]. Additionally, we have found that the reliability of the ERN does not differ between clinically anxious and healthy populations [26]. This work validates the use of the ERN as a reliable biomarker in clinical and developmental populations and lays the foundation for the diagnostic use of the ERN in clinical settings.

The ERN—a diagnostic tool?

According to the Biomarkers Definition Working Group [2], a biomarker should be able to be used as a "diagnostic tool for the identification of those patients with a disease…and as a tool for classification of the extent of the disease." Indeed, the ERN is increased in individuals with clinical anxiety disorders [13] and relates to dimensional measures of anxiety symptoms (even within clinical populations; [10]), thereby indexing the extent or severity of the disorder. Recently, we have completed ROC curve analyses to determine a clinical cutoff score for the ERN that predicts GAD group membership with sensitivity and specificity that is at par or superior to many self-report measures [26]—predicting approximately 26 % of the variance in GAD group membership. Given that the ERN can be measured quickly (in under 10 min) and cheaply, it has potential utility in clinical or diagnostic settings—although more work is needed to develop norms and standardized ways of measuring the ERN.

The ERN as an index of risk for anxiety

In addition to being able to index current disease state, a biomarker may also be useful in detecting who is *at risk* for developing a disease. Our work and others has found support for the notion that the ERN may index risk for anxiety disorders. The ERN is stable and trait-like in adults and children [28, 30, 31], as well as heritable [32]. In addition, healthy first-degree relatives of individuals with anxiety disorders display an elevated ERN [33, 34]. Important to the use of a biomarker that can track pathological trajectories *early* in development, the ERN can be measured in young children [35]. We recently found that an increased ERN in 6-year-old children predicts the onset of new anxiety disorders 3 years later, while controlling for baseline anxiety symptoms [36•]. Furthermore, we have extended this work and found that children with an elevated ERN are particularly prone to environmentally induced increases in anxiety symptoms; in a large sample of children who experienced Hurricane Sandy, it was the children who were high in temperamental fear *and had an increased ERN* who displayed post-hurricane symptom increases [37]. Two other prospective studies have also found that the ERN interacts with fearful temperament to predict risk for anxiety across development [38, 39]. More work is needed to identify developmental norms for the ERN so that children who are most at risk for developing pathology can be identified in various age ranges. Additionally, this work needs to be extended to adults; whether the ERN can predict new onset disorders in adulthood has not yet been determined. Future work should examine this question in adult

populations who are at risk for new-onset anxiety disorders (e.g., first responders or individuals in the military).

Animal models of error processing

One of the main uses of a biomarker, as stated by the Biomarker Definition Working Group (2001), is to serve as a *clinical endpoint* that can be used to evaluate pharmacological interventions in animal models. Along these lines, a biomarker should be mechanistic—indexing processes closely linked to the cause of the illness such that manipulations that affect the biological substrates implicated should alter both the illness in a patient and physiology in a model organism [40].

A meta-analysis combining data from 15 source localization studies in humans found a source for the ERN in the anterior cingulate cortex (ACC; [41]). This is consistent with findings from human intracranial recordings [42] and functional magnetic resonance imaging (fMRI) studies [43–45] that find error activation in the ACC. Likewise, single-unit recording studies in monkeys demonstrate error-related ACC activity [46, 47], and intracortical field potentials recorded in the ACC of rodents have been shown to display error-modulated activation similar to humans [48]. Furthermore, in rodent models, researchers have used muscimol to temporally inactivate the ACC, leading to altered error-related ACC activation and subsequent behavioral changes [48]. An exciting avenue for future work is to identify pharmacological interventions that may target error-related ACC activation in non-human primates or rodents to reduce trait anxiety. Such pharmacological interventions may have cross-species applications for reducing or preventing anxiety disorders in humans.

The ERN as a treatment target

In addition to being used as a diagnostic tool, a biomarker may also serve as a clinical endpoint insofar as it might become the *target* of treatment. This may introduce novel treatment approaches—for example, much progress has been made using antiretroviral therapy to target a biomarker of HIV (messenger ribonucleic acid viral load). We have recently begun to examine behavioral and cognitive interventions that may target the ERN. In one study, we found that participants who completed an attention bias modification (ABM) program designed to train individuals to disengage their attention from threatening stimuli and increase attention toward neutral or positive stimuli displayed a reduced ERN [49]. Ongoing research in a large sample of adolescent girls will determine if multiple ABM training sessions can reduce the ERN and thereby risk for anxiety across development.

We are also examining intervention strategies focusing on parenting with the aim of altering the ERN in offspring. We have found that the ERN can be increased in the lab (e.g., by using a loud noise as punishment for error commission; 50]. Building on this finding, we found that harsh or punishing parenting styles (measured both observationally and via self-report) are related to an increased ERN in young children [51]. Moreover, we found that an increased ERN mediated the relationship between harsh

parenting and anxiety disorders in children, suggesting that the ERN may be one mechanism whereby parenting impacts anxious outcomes in children. We are currently following up on these findings to determine if intervention strategies focusing on parenting styles may alter children's ERNs and thereby anxiety symptoms.

Conclusion and future directions

The current review evaluated one psychiatric biomarker in an attempt to outline a roadmap for the development of future biological markers of risk for psychopathology. Our work (and others) suggests that the ERN relates to diagnostic status, as well as dimensional symptom measures, and this relationship is evident early in the course of development. Additionally, the ERN relates to current disease state and can predict risk for developing psychopathology over time. The ERN can differentiate highly comorbid clinical diagnoses (e.g., anxiety and depression), and indexes a specific transdiagnostic and clinically relevant phenotype (i.e., checking symptoms). The ERN displays excellent psychometric properties and can predict a substantial amount of variance in clinical outcomes. Animal models of error processing open up promising avenues for future intervention development and we have begun to develop novel behavioral intervention strategies that target the ERN (attentional training and parenting interventions). The identification of this biomarker, and novel treatment target opens up exciting directions for future work—such as using neurostimulation techniques to more directly alter error-processing networks [52, 53]. An important next step in this work is examining to what extent altering a neural biomarker (e.g., the ERN) can alter symptoms and long-term trajectories of risk for disorders.

Compliance with Ethical Standards

Conflict of Interest
Alexandria Meyer declares that she has no conflict of interest to disclose.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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