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The Utility of Event-Related Potentials in Clinical Psychology

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Keywords

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Abstract

Event-related potentials (ERPs) are direct measures of brain activity that can be leveraged for clinically meaningful research. They can relate robustly both to continuous measures of individual difference and to categorical diagnoses in ways that clarify similarities and distinctions between apparently related disorders and traits. ERPs can be linked to genetic risk, can act as moderators of developmental trajectories and responses to stress, and can be leveraged to identify those at greater risk for psychopathology, especially when used in combination with other neural and self-report measures. ERPs can inform models of the development of, and risk for, psychopathology. Finally, ERPs can be used as targets for existing and novel interventions and prevention efforts. We provide concrete examples for each of these possibilities by focusing on programmatic research on the error-related negativity and anxiety, and thus show that ERPs are poised to make greater contributions toward the identification, prediction, treatment, and prevention of mental disorders.

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INTRODUCTION

If medicine had limited itself to self-report assessments of symptoms, mechanism-based treatments of illness would have languished. Neuroscience methods are increasingly used in psychiatry and clinical psychology, a trend that reflects the general sense that the brain is the right organ to study in the search for biological causes of, and mechanism-based interventions for, mental disorders (Insel & Cuthbert 2015, Jones & Mendell 1999). We even presume that the impact of experience and the environment on psychiatric outcomes is determined, at least in part, by changes in the structure and function of the brain (Bremner 2002). Although it may not be possible to reduce mental illness solely to differences in neural activity (Miller 2010), neuroscientific measures are attractive insofar as they are more objective than some of the traditional ways psychologists and psychiatrists have approached mental disorders: Neuroscience-based differences and abnormalities seem to suggest possible new causes and routes to novel interventions.

And yet human neuroscience studies have produced few, if any, innovations in the diagnosis and treatment of mental illness (Insel et al. 2010, Stringaris 2015). For example, for many years there was a sense that the field was going to solve the problem of anxiety disorders by focusing on the amygdala (Rauch et al. 2003). But what is the clinical utility of amygdala activity or any human neuroscience measure for that matter? Can neuroscientific methods be clinically meaningful?

The current review focuses on the clinical utility of event-related brain potentials, or ERPs. ERPs are direct measures of brain activity that can be used to study distinct neural processes within

and across individuals. To make more general points about the potential clinical utility of ERPs, we focus on one exemplar: increased error-related brain activity in relation to anxiety disorders. We consider specific ways in which ERPs can be useful in clinical psychology and psychiatry: from transdiagnostic neural correlates derived from cross-sectional between-participant studies to neural biomarkers of risk that predict psychopathology in longitudinal research to novel targets for interventions. In this context, we provide an overall road map to guide neuroscientific studies toward clinical utility and suggest ways in which ERP data might be further leveraged in the future.

EVENT-RELATED POTENTIALS: OVERVIEW

Basics of Recording, Timing, and Scalp Distribution of Event-Related Potentials

Neurons communicate through chemical and electrical changes, for example, through neurotransmitter binding and postsynaptic potentials, respectively. The ongoing electrical activity of the brain that can be recorded noninvasively at the scalp is reflected in the electroencephalogram (EEG). The electrical activity is often sampled rapidly (e.g., every millisecond) and recorded by electrodes placed at many sites across the scalp that are usually embedded in elastic mesh caps worn by participants. These electrode sites are named in accordance with the 10–20 system that uses a combination of letters and numbers to define locations. For example, F refers to frontal, C to central, and P to parietal; odd and even numbers indicate, respectively, left or right of midline, and the midline is referred to as zero, or zed, and indicated with a z. Thus, Fz would refer to the midline frontal electrode site.

At all points in time, the EEG at every electrode site is impacted both by meaningful changes in brain activity as well as various sources of noise; therefore, it is difficult to interpret. One way to leverage the EEG to better understand brain function is to examine the EEG when it is time-locked to specific events of interest. The logic is that these events will cause large groups of neurons to become active in synchrony, and the resulting postsynaptic potentials can summate, propagate through the brain, and will be evident in the EEG at specific points in time. When the EEG is time-locked to specific events, the resulting electrical changes are referred to as event-related potentials, or ERPs (Luck & Kappenman 2011).

Throughout the current review, we focus on error-related brain activity to illustrate more general points about the potential clinical utility and promise of ERPs. To elicit error-related brain activity, we have participants perform speeded response tasks on a computer, and we have often utilized an arrowhead version of the flankers task. On each trial, participants must respond to the direction of a central arrowhead that is flanked by either compatible (i.e., "< < < < <", "> > > > >") or incompatible (i.e., "< < > < <", "> > < > >") arrowheads. Stimuli are presented briefly (i.e., for 200 ms), and participants perform between 300 and 400 trials during approximately 10 minutes. In the context of the preceding discussion, the EEG can be time-locked to many events: the presentation of the imperative stimuli or the execution of both correct and incorrect responses. Although we focus on ERPs that are time-locked to responses, it is also possible to examine stimulus-locked ERPs during this task.

It is important to note that even ERPs reflect a mix of meaningful brain activity and noise. To illustrate this point, **Figure 1*a*** contains two segments of the EEG from a single participant at the FCz electrode site that is time-locked to the onset of a single correct response and a single error response; the average ERP for 20 correct and 20 error responses for this same participant are presented in **Figure 1*b***. By averaging many segments together, time-locked to the same or similar events, signal is increased and noise is decreased. In terms of the latter, consider the baseline period in **Figure 1**: Whereas there is apparent ERP activity prior to the response after one trial (*a*), this

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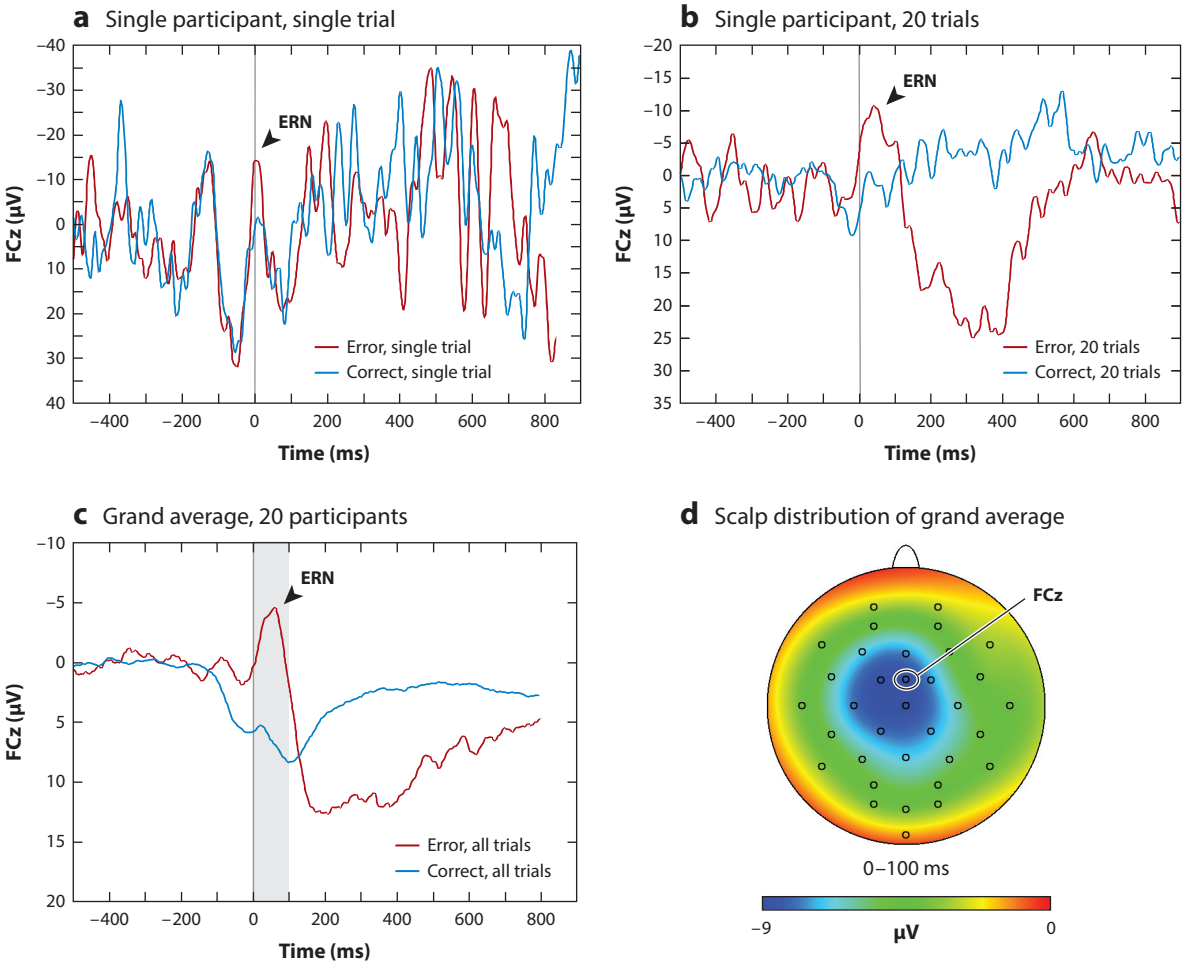

Figure 1

Event-related potentials (ERPs) from an arrows version of a flankers task. (*a*) Response-locked ERPs at the frontocentral midline (FCz) for a single correct trial and an error trial from a single participant and (*b*) from the same participant after 20 error trials and 20 correct trials were added to the ERP average. (*c*) ERPs from 20 participants for correct and error trials are presented, as well as (*d*) the scalp distribution of the difference between error and correct trials in the highlighted time window (i.e., 0–100 ms) of the error-related negativity (ERN).

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activity summates toward zero after many trials are averaged together (*b*). However, postresponse activity in the ERPs does not summate toward zero after averaging many trials together because it is meaningful and not random. Most ERP studies present group-level averages, and **Figure 1*c*** portrays the grand average (i.e., the average of many participants' averages) for 20 participants.

ERPs are defined by specific features: the experimental factors that produce variability in the ERP (e.g., error versus correct responses), polarity (i.e., whether an ERP is a relative negativity or positivity), timing (i.e., when the ERP is maximal relative to an event of interest), and scalp distribution (i.e., where on the head the ERP is maximal) (Keil et al. 2014). Putting it all together then, the error-related negativity (ERN) is a response-locked negativity at the frontocentral recording site (i.e., FCz) that is maximal approximately 50 ms after error compared with correct responses.

Figure 1*d* plots the mean activity occurring between 0 and 100 ms for the difference from the grand average between error and correct trials at each electrode site: The central area depicts the frontocentral negative maximum for the difference between errors and correct trials in the time range of the ERN.

Advantages of ERPs

Electrocortical activity is measured at the scalp in terms of voltage changes; thus, ERPs are direct measures of neural activity: Brain activity evident in ERPs is not inferred from statistical models, as is the case for most analyses that employ functional magnetic resonance imaging (fMRI). Although several processing steps can be applied to improve signal and isolate it from unwanted noise, simply averaging EEG segments is often sufficient to visualize ERPs. Specific ERPs are generally evident in single-participant averages, as is shown in **Figure 1**. In this way, ERPs tend to be robust and reproducible. As far as neuroscientific measurement goes, ERPs also have excellent temporal resolution. Because the electrical activity can be sampled rapidly (e.g., every millisecond) and because ERPs reflect near-instantaneous changes in electrical brain activity, it is possible to measure and parse many early neural responses. For instance, **Figure 1*c*** indicates that the ERN is followed by a relative positivity, such that multiple ERPs are evident within just a few hundred milliseconds after participants make mistakes.

ERPs also have many practical advantages as measures of brain activity: They are relatively cheap and fast to collect; data collection itself is portable, can be administered in a variety of settings, and does not require particularly extensive training; file size makes storage nonprohibitive; data can be analyzed relatively quickly; ERPs can be measured across a wide-range of ages (e.g., very young to very old) and have relatively few contraindications (e.g., unlike with MRIs, claustrophobia, as well as orthodontic braces and other metal in the body, are not contraindications).

As described above, ERPs are defined by features from within-person contrasts. The ERN, for instance, is defined in terms of ERP differences evident between error and correct trials, and this is a within-person comparison. However, clinical psychology requires measures that can shed light on individual differences; for example, we want to understand why some people are more anxious or depressed than others. Thus, not only is the ERN a distinct neural response to making mistakes, it also appears to reflect meaningful individual differences in how people respond to errors (Weinberg et al. 2012b, 2016). That is, people vary in the size of their ERN, and this variability has been linked to clinically meaningful constructs (described more fully below).

This move from within- to between-participant comparisons requires measures with good psychometric properties (Hajcak et al. 2017), and researchers have begun to report both the internal consistency and test–retest reliability of ERPs. In the context of the ERN, we have found that it has excellent internal consistency both in adults (i.e., split-half reliability between 0.70 and 0.90; Foti et al. 2013; Olvet & Hajcak 2009a,b; Riesel et al. 2013) and children (i.e., split-half reliability between 0.60 and 0.90; Meyer et al. 2014), and it has good test–retest reliability over periods that range from weeks (i.e., $r = 0.70$ to 0.74; Olvet & Hajcak 2009a) to years (i.e., $r = 0.60$ to 0.70; Meyer et al. 2014, Weinberg & Hajcak 2011). Given the increasing number of multisite studies, it will be important for future studies to also assess the reliability of the ERN across sites (e.g., using a traveling participants study). Although to the best of our knowledge this has not yet been done, we have assessed ERNs in the same 20 participants using different EEG hardware. Specifically, we measured the ERN in the same flankers task using two active electrode EEG systems [i.e., BioSemi (Amsterdam, the Netherlands) and Brain Products (Gilching, Germany)] and found that the ERNs were highly correlated ($r \approx 0.70$) and had similarly high internal consistency (both Cronbach's $\alpha \approx 0.80$), suggesting that ERP measures may be fairly comparable across different

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EEG systems. Finally, we would argue that one advantage of ERPs is their demonstrated clinical utility: As described below, ERPs can be used to differentiate clinical groups and predict the onset of psychiatric disorders.

Disadvantages of ERPs

Compared with other measures of neural activity, such as those derived from fMRI, it is more difficult to make exact claims about the specific neural sources or neural generators of ERPs. For instance, it has been suggested that the ERN is generated in the anterior cingulate cortex (ACC) (Cavanagh et al. 2010, Debener et al. 2005, Ridderinkhof et al. 2004), although others have suggested the involvement of the posterior cingulate cortex and presupplementary motor area (Grützmann et al. 2016, Shackman et al. 2011). ERPs may well reflect something more akin to network activation than the kind of specific localization of function that dominated early cognitive neuroscience.

Although ERPs are robust and reproducible, the exact psychological meaning of ERPs is often debated, even decades after the discovery and initial characterization of an ERP. The ERN, for instance, was first reported on in the early 1990s (Falkenstein et al. 1991, Gehring et al. 1993). Even now, its exact function is actively discussed, and no single account of the ERN is accepted by the entire field; for instance, the ERN has been linked to both error and conflict detection (Gehring et al. 2018). Although the ERN has robustly been related to individual differences in anxiety, the specific interpretation of this relationship is debated (Proudfit et al. 2013).

Although ERPs reflect direct neural activity, many choices must be made during data processing and analyses. The EEG is often filtered to reduce activity at frequencies outside the range of possible interest. ERPs reflect the electrical potential between two places; thus, when an ERP is defined as being maximal at FCz, this really implies the difference between FCz and the reference site. ERP researchers typically use either mastoids or the average activity at all sites as the reference. One of the largest sources of artifact in the EEG comes from blinks and other eye-related movements; blinks, for instance, can produce activity at the scalp that is 10 times larger than an ERP of interest. There are several accepted methods for dealing with ocular artifacts that range from regression-based correction approaches to independent component analysis to excluding trials with blinks. Each method has its advantages and disadvantages. Overall then, ERPs in a given study result from several somewhat idiosyncratic decisions about data processing, and although there is good guidance on reporting these details and the range of sensible choices (Keil et al. 2014), there is no single gold standard set of data analytic decisions.

Quantifying ERPs means weighting some data points and not others. For instance, the ERN is often scored as the average activity occurring from 0 to 100 ms after response onset at FCz (i.e., where and when the difference between error and correct trials is maximal). However, it is also possible to score the ERN using peak measures or using the area around the peak, and this can be done at a single site (e.g., FCz) or across several sites (i.e., averaging multiple electrode sites together). Each scoring approach essentially amounts to a slightly different way of weighting the ERP data. Given the number of electrode sites, time points, and options for ERP scoring, one possible disadvantage of ERPs is the potential for type I errors.

One final disadvantage of ERPs follows directly from their excellent temporal resolution: Individual ERPs can overlap with one another, and variability in one ERP can produce apparent variability in another. Kappenman & Luck (2011) provide a compelling argument for using condition-related difference scores to overcome component overlap. More complex alternatives include using factor analytic approaches, such as principal component analysis, to parse overlapping ERPs (Foti et al. 2011).

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ERPs: CORRELATES OF INDIVIDUAL DIFFERENCES

Between-Group Comparisons

A classic experimental design in clinical neuroscience is to compare one group of individuals that has the diagnosis of a disorder with another group of individuals that does not meet the criteria for any diagnosis: Neural differences between the two groups are then interpreted as being meaningfully related to the disorder. As an example, Gehring and colleagues (2000) first reported that the ERN was increased among patients diagnosed with obsessive–compulsive disorder (OCD). Conceptually, these data were taken to reflect abnormal error signals that might underlie symptoms in OCD, such as repeated checking and the sense that something is wrong. Since 2000, more than 20 studies have replicated this finding and suggested that an increased ERN is a robust neural correlate of OCD (Endrass & Ullsperger 2014, Meyer 2016).

It is important to keep in mind that these studies tend to report statistically significant differences between group means. At the level of individuals, however, some controls might look more like they belong in the disordered group and vice-versa (i.e., there is overlap between the distribution of the ERN in diagnostic versus control groups). In the context of the ERN studies described above, it would certainly be possible, for instance, to find a patient with OCD who has a smaller ERN than a participant with no diagnosable psychopathology. Later in this review, we provide concrete examples of how this follows if the ERN is determined both by multiple phenotypes and unexpressed genetic risk for different forms of psychopathology.

Relatively simple between-group studies leave many questions unanswered, for instance, could group differences reflect comorbid diagnoses or more general impairments caused by a given disorder? In the context of the previous discussion, is an increased ERN specific to OCD? And if not, what other disorders are characterized by an increased ERN? In this way, one can ask how a particular ERP carves up the space of psychopathology—that is, how the ERN varies with diagnostic boundaries articulated in the *Diagnostic and Statistical Manual of Mental Disorders* (Am. Psychiatr. Assoc. 2013). Indeed, an increased ERN has now been reported both among individuals with generalized anxiety disorder (GAD) (Weinberg et al. 2010, 2012a, 2015) and those with social anxiety disorder (SAD) (Endrass et al. 2014). Some studies have simultaneously assessed multiple groups and found that patients with OCD are characterized by an increased ERN that is similar in magnitude to the increased ERN in patients with GAD (Weinberg et al. 2015, Xiao et al. 2011), patients with SAD (Endrass et al. 2014), and patients with health-related anxiety (Riesel et al. 2017).

Although the ERN has been robustly related to OCD and specific anxiety disorders (i.e., GAD and SAD), its relationship with major depressive disorder (MDD) has been mixed. This is particularly perplexing insofar as MDD is frequently comorbid with OCD, GAD, and SAD, and some have even argued that GAD and MDD are actually the same distress disorder (Watson 2005). In a series of studies, we found that concurrent MDD actually suppresses the relationship between the ERN and GAD. That is, we found that adults with diagnosed GAD without comorbid current MDD were characterized by an increased ERN; however, those GAD patients with comorbid MDD did not have an ERN that differed from healthy controls (Weinberg et al. 2012a). We found the same suppressive relationship of MDD when we examined the ERN in patients with OCD (Weinberg et al. 2015).

These data suggest that commonly comorbid disorders can have an opposing impact on ERPs. Even though some have suggested that GAD and MDD are indistinguishable distress disorders, these disorders have a distinct impact on neural function as indexed by the ERN. In this way, ERPs might provide input for structural models of psychopathology. These results further suggest that an increased ERN in GAD, OCD, and SAD does not simply reflect psychological distress or broad impairment, otherwise one would expect to reliably see an increased ERN in MDD.

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Many individuals with diagnosable psychopathology are receiving some form of treatment, which raises the possibility that treatment—especially pharmacological—could cause apparent group differences in ERPs. In terms of experimental design, this might be avoided by including only patients with current diagnoses who are not also taking medication. This would not, however, rule out the possibility that ERP differences could result from having taken certain medications for many years (e.g., a scar, caused by medication).

In terms of the ERN, Stern and colleagues (2010) demonstrated that patients with OCD are characterized by an increased ERN regardless of whether they are taking medication. Along similar lines, experimental work has found that the short-term administration of drugs typically used to treat anxiety and depression [i.e., selective serotonin reuptake inhibitors (SSRIs)] does not impact the ERN (De Bruijn et al. 2006). However, evidence does suggest that the ERN is impacted by the acute administration of some dopaminergic drugs (De Bruijn et al. 2004, 2006), as well as caffeine (Tieges et al. 2004) and alcohol (Bartholow et al. 2012). Overall then, between-group studies that include medicated patients need to carefully consider the current, and potentially past, use of psychoactive medications and other compounds.

Continuous Variability

Studying groups of individuals with diagnosed psychopathology is a categorical approach to understanding individual differences; these studies essentially assume that there are only two types of individuals: those with a disorder and those without a disorder. Imagine someone who almost meets the diagnostic criteria for GAD; a between-group study might treat this person as a healthy control even if they are more anxious and worried than an average person. An alternative approach is to examine the relationship between an ERP of interest and continuous variability on symptoms, traits, or other measures of individual difference. Statistically, this is akin to a correlational approach rather than a between-samples comparison of means. Recent efforts, such as the Research Domain Criteria, highlight the potential pitfalls of using dichotomous, diagnosis-based studies and emphasize examining transdiagnostic and continuous variability instead (Cuthbert & Kozak 2013, Insel et al. 2010).

As an example, rather than focusing on individuals diagnosed with GAD, a continuous approach to individual differences might relate the ERN to self-report anxiety scores in a large group of individuals drawn from a psychological clinic or from the community, regardless of their current diagnoses. This approach would, therefore, include individuals across the full range of anxiety severity, including those with high, low, and medium scores. Indeed, multiple meta-analyses have confirmed that the ERN relates to continuous variability in self-report levels of trait anxiety (Cavanagh & Shackman 2015), with a medium effect size ($r \approx 0.30$ or Cohen's $d \approx 0.63$). These data are broadly consistent with the between-group studies reviewed above, insofar as multiple disorders characterized by high trait anxiety (e.g., OCD, GAD) have been shown to have an increased ERN. These data also suggest that having a clinical diagnosis (i.e., having GAD or OCD) is not necessary for observing an increased ERN.

One of the advantages of taking a continuous approach to understanding individual differences is that it is possible to ask simultaneously about the relationship between an ERP of interest and multiple phenotypes. For instance, one could examine which aspects of depression an ERP is most related to: sleep or appetite disturbance, low mood, or anhedonia. One additional advantage of this approach is that it becomes possible to study neural processes across diagnostic boundaries (e.g., sleep disturbance is characteristic of disorders other than depression). In the same sample in which we found that a categorical diagnosis of MDD suppressed the relationship between a categorical diagnosis of GAD or OCD and an increased ERN, we also found that a larger ERN was predicted

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by continuous variability in both checking and depressive symptoms but in opposite directions: An increased ERN was independently related to increased checking symptoms and decreased symptoms of psychomotor retardation (Weinberg et al. 2015). In a separate large sample of community adolescents, we replicated this general pattern, and we again found that an increased ERN was related both to increased checking symptoms and decreased depressive symptoms (Weinberg et al. 2016).

Insights and Issues

The relationship between constructs of individual difference and a specific ERP measure is most likely to be many to one; that is, a single ERP will be impacted by multiple traits and states. Using both between-group and continuous measures, we have consistently found that the ERN is independently related to individual differences in both anxiety and depression. Although we focus on the ERN–anxiety relationship for the remainder of this review, it is also worth pointing out that attention-deficit/hyperactivity disorder, substance use disorders (SUDs), and related externalizing traits have been linked to a reduced ERN (Hall et al. 2007, Luijten et al. 2014, Shiels & Hawk 2010). The overarching point here is that a given ERP will likely be impacted simultaneously by multiple phenotypes. Moreover, correlated phenotypes can impact an ERP in opposing ways: through suppressor effects that can be demonstrated by using carefully designed between-group comparisons or by using continuous measures in large samples employing regression-based analyses.

It is worth noting that a relatively small amount of variance in clinical outcomes is related to a given ERP. In both between-group and continuous measure studies of the ERN, effect sizes tend to be consistent and moderate: Approximately 10% of the variance in current anxiety (either in continuous or dichotomous study designs) is accounted for by variability in the ERN. In our view, an association of this magnitude (or smaller) is about what the field ought to expect (Patrick et al. 2013), especially since ERPs are impacted by multiple individual difference factors and share no method variance with self-report or interview-based measures. One additional possibility that we have discussed previously is the notion of combining multiple ERPs (Hajcak et al. 2017, Patrick & Hajcak 2016), much the way that several subscales make up a self-report index; for an example of such an approach in the domain of genetics, see Bogdan et al. (2018).

Rather than conceptualizing an ERP as a scale, it may make more sense to think about it as an item, or subscale, that can be leveraged in concert with other ERPs and measures of individual difference (Patrick & Hajcak 2016). As one concrete example, we used spectral analysis to quantify error-related brain activity. Similar to other studies, we found increased error-related activity in the 4–8 Hz range (i.e., theta band); moreover, this frequency-based representation of error-related brain activity was uncorrelated with the ERN, and both the ERN and error-related theta were uniquely related to GAD status. Incorporating time–frequency measures allowed us to account for nearly 25% of between-group variance (Cavanagh et al. 2017). Thus, it is possible to use multiple neural metrics derived from the same EEG data to better classify individuals (Nelson et al. 2018). We later describe concrete examples of how even a single ERP can be applied in combination with self-report measures to better identify those at highest risk for anxiety.

ERPs: MEASURES OF RISK FOR PSYCHOPATHOLOGY

Studies of Individuals at High Risk

Once an ERP has been shown to be reliably associated with psychopathology and related individual differences, this gives rise to another major question: Do alterations in the ERP precede

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the onset of the disorder or are they evident only following disorder onset? This question is also relevant to the notion of an endophenotype, which is a relatively simple and unobservable trait that mediates part of the complex pathway from genetic vulnerably to the overt expression of a disorder (Gottesman & Gould 2003, Miller & Rockstroh 2013). For a measure to function as an endophenotype it should be robustly associated with a disorder, heritable, independent of current symptom state, and occur at higher rates within affected families (Gottesman & Gould 2003).

The ERN has been discussed as a potential endophenotype for 10 years (Hajcak et al. 2008, Olvet & Hajcak 2008). Anokhin and colleagues (2008) estimated that 30% to 50% of the variability in the ERN was genetically heritable. Around the same time, the first treatment study found increased ERN amplitudes before and after successful cognitive behavioral therapy (CBT) in pediatric OCD (Hajcak et al. 2008). Thus, about a decade ago, the ERN seemed to satisfy most of the criteria for an endophenotype.

Since that time, further support for the endophenotype account of the ERN has come from studies in unaffected relatives. Riesel and colleagues (2011) demonstrated for the first time that healthy relatives of patients diagnosed with OCD had increased ERNs; indeed, relatives of people with OCD had ERNs comparable to those of the patients themselves, and ERNs in both groups were significantly different from those of a healthy control group. Carrasco and colleagues (2013) replicated these results and found increased ERNs in unaffected siblings of adolescents with OCD. Moreover, in a recent study with a considerably larger sample, we replicated the finding of increased ERNs in unaffected first-degree relatives of patients with OCD (Riesel et al. 2018). In this study, the family history of psychopathology was also assessed in a group of healthy controls, and Riesel and colleagues (2018) found higher ERN amplitudes among first-degree relatives of individuals with mixed anxiety diagnoses and decreased ERN amplitudes in healthy participants with a familial risk for SUDs. These findings further validate increased ERN amplitudes as an endophenotypic risk marker for OCD, and they also suggest that both increases and decreases in the ERN represent transdiagnostic risk markers for several disorders along an anxiety–impulsivity spectrum (Gillan et al. 2017).

Together these studies convincingly suggest that the ERN fulfills the necessary criteria to be regarded an endophenotypic risk marker. Indeed, the ERN has been linked to specific polymorphisms related to dopamine (*DRD2,DRD4*, *DAT1*, *COMT*), serotonin (*5-HTTLPR*, *5Ht1A*), and brain-derived neurofactor (*BDNF*) (Manoach & Agam 2013). The endophenotype concept has been criticized recently, mostly for not being helpful in the search for specific genes linked to psychiatric disorders (Iacono 2018, Iacono et al. 2017). Nonetheless, the endophenotype approach has proven fruitful for guiding research that has systematically tested the utility of ERPs as risk indicators for complex, genetically determined psychiatric disorders. As described in the next section, prospective studies further confirm the importance of the ERN in terms of risk.

Prospective Studies

The type of risk-related studies described above, in which the ERN is linked to risk through designs exploring family history, are cross-sectional in nature, and having a first-degree relative with a disorder is an imperfect indicator of risk. Another way to relate a measure to risk is through using large samples and longitudinal experimental designs to determine whether ERPs can predict actual changes in symptoms over time. These studies are expensive and time-consuming, and we would argue that they should be undertaken only after a reasonable accumulation of data suggests the potential value of such a study.

We first reported that an increased ERN in 6-year-old children predicts the onset of anxiety disorders 3 years later, when the children are approximately 9 years old (Meyer et al. 2015a).

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When using ERPs to predict who is at risk for developing psychopathology, it is imperative to examine whether the ERP provides incremental predictive ability. For example, we controlled for other risk factors (i.e., maternal history of anxiety and baseline anxiety symptoms in the child) and found that the ERN had unique predictive power in delineating which children would become anxious between the ages of 6 and 9 years old (Meyer et al. 2015a). We have recently replicated this pattern of results in a large sample of adolescent girls, finding that the baseline ERN predicts new onset of GAD, even when controlling for other baseline measures linked to risk (Meyer et al. 2018c). In these studies, an ERP was used to predict changes in diagnostic status. Other work suggests that ERPs may also be helpful in predicting changes in dimensional symptoms (Nelson et al. 2016). Future work should examine to what extent combinations of ERPs may predict both new-onset diagnoses as well as increases in measures of continuous symptom domains.

Some work has also shown that ERPs can be useful in delineating developmental trajectories by acting as moderators. For example, we know that children characterized by increased behavioral inhibition are at increased risk for developing anxiety disorders, but most will actually remain healthy (Buss & Kiel 2013). ERPs can help delineate clinical from nonclinical trajectories, even among individuals at increased risk. For example, two studies suggest that the ERN moderates the association between early behavioral inhibition and anxiety disorders later in life, such that children characterized by increased behavioral inhibition and an increased ERN are most at risk for anxiety disorders (Lahat et al. 2014, McDermott et al. 2009).

In addition to using ERPs to predict the general risk for psychopathology, ERPs may be used to better understand who will experience increases in symptoms in response to stressful life events. This may be especially useful in populations that are likely to experience a stressful event (e.g., pregnant women, individuals in the military, first responders). In a recent study, we found that among children who experienced a stressful life event (i.e., Hurricane Sandy), those with a higher baseline ERN were more likely to experience post-hurricane increases in anxiety symptoms (Meyer et al. 2017).

It is worth noting that there is also evolving evidence for the predictive utility of the ERN for disorders characterized by disinhibition. Anokhin & Golosheykin (2015) found that a reduced ERN measured at age 14 prospectively predicted the initiation of tobacco use at age 18. This is in line with the findings from healthy children at high risk for SUD (Euser et al. 2013), indicating that error-monitoring deficits characterized by decreased ERN amplitude are likely to be a risk marker for SUD that precedes the development of the disorder. Thus, both the over- and under-recruitment of the error-monitoring system seem to be associated with risk for different types of disorders (Riesel et al. 2018).

Insights and Issues

Relying solely on self-report and interview measures for risk detection is limited insofar as it is possible only to assess symptoms that an individual is already experiencing (or has experienced in the past); and using reported family history is imprecise. There is a need to identify those who are at risk prior to the onset of disorders, especially young children for whom early intervention strategies are more effective (Mancebo et al. 2014).

Both studies of those at high risk and prospective studies indicate that ERPs can help to identify who is at increased risk for psychopathology even when accounting for baseline symptoms. It may be possible to use ERPs to identify who is most at risk for increases in symptoms after stressful life events or traumas and to use this information to implement preventive strategies.

As with between-participant variability, any single ERP may predict only a small-to-moderate amount of variance in outcomes. As described above, it is possible to combine multiple EEG-based

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measures to better predict risk (Nelson et al. 2018). Moreover, multiple EEG-based measures or a corresponding biosignature can be used in conjunction with known and established risk factors (e.g., symptoms, history of psychopathology) to better identify individuals at the greatest risk (Nelson et al. 2016, 2018). For instance, we recently demonstrated that the ERN provides incremental positive predictive value for new-onset GAD when applied in combination with baseline symptoms (Meyer et al. 2018c). A decision-making algorithm requiring that individuals be counted as positive if they met a threshold for baseline symptoms (+1.5 SD) and ERNs (+2.0 SD) exhibited good positive predictive value (72%) and excellent negative predictive value (94%) compared with values of approximately 64% for positive and negative predictive value when using either measure in isolation. This approach also exemplifies how ERPs might be used in the real world: Rather than collecting EEG data from everyone, it might make the most sense to examine risk-related ERPs only among individuals who exceed a threshold on another measure that is even easier to administer. In terms of prediction, the goal is to identify ERPs that predict risk over and above symptoms and then establish thresholds and recommendations for risk detection. In the case of developmental risk markers, ERP cutoffs (i.e., norms) will need to be determined based on age, especially since many ERPs change throughout development. Additionally, more work is needed to identify standard tasks that can be used to elicit ERPs in the most efficient way possible in applied settings, so that ERPs can be compared across settings, and standard thresholds can be utilized. This is especially challenging in developmental populations, wherein different tasks may be necessary at different ages because of a task's difficulty.

ERPs: DEVELOPMENTAL MECHANISMS OF RISK

Developmental Changes and Models

ERPs are ideal for charting developmental trajectories of both normative development and psychopathology insofar as they can be administered quickly and easily to children, are more resilient to movement artifacts, and have fewer contraindications compared with other neural measures (e.g., fMRI). Indeed, many ERPs have been used to study neurodevelopmental processes. As just as one example, the magnitude of the ERN has been shown to increase across childhood and adolescence, plateauing in early adulthood (Tamnes et al. 2013). Recent work has demonstrated that age-related changes in the ERN are at least partially due to increases in hormone levels during puberty (Gorday & Meyer 2018), suggesting a potential mechanism through which adolescent development impacts behavior through changes in the brain.

Although ERPs may change throughout development, they can be measured early in childhood. An increased ERN in relation to anxiety in children has been reported in several studies (Hajcak et al. 2008, Ladouceur et al. 2018, Meyer et al. 2013). Indeed, children as young as 6 years old with clinical anxiety display an increased ERN (Meyer et al. 2013). Moreover, the ERN can be measured in children as young as 4 years old and has been linked to individual differences in early temperament (Brooker & Buss 2014), and a number of studies have linked early behavioral inhibition with an increased ERN later in childhood (Lahat et al. 2014, McDermott et al. 2009, Meyer et al. 2018b, Torpey et al. 2013). These data suggest that the ERN may be useful in characterizing early emerging developmental trajectories toward increased anxiety; moreover, they confirm that the ERN–anxiety link is evident relatively early in life.

Using ERPs to measure brain activity across childhood may also inform developmental models of psychopathology. For example, while many theoretical models emphasize developmental changes in fear (Casey et al. 2008, Ernst et al. 2006), most fail to consider potential changes in the phenomenological manifestation of fear throughout development. In our work using the ERN, we have been able to characterize one such shift. We were surprised by initial findings that young

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children with increased temperamental fear had a decreased ERN (Torpey et al. 2013). By using a within-participant design, we have subsequently shown that children with increased temperamental fear had a decreased ERN when they were 6 years old, but by age 9, those same fearful children displayed an increased ERN, a pattern that more closely resembles that of anxious adolescents and adults (Meyer et al. 2018b). That is, increased temperamental fear was associated with a decreased ERN at age 6 and an increased ERN at age 9: Temperament determined the developmental trajectory of neural systems implicated in error monitoring.

We have suggested that the ERN tracks the developmental transition from fear of external threat in relatively young children (e.g., the darkness of the room, the experimenter, being separated from parents) to self-conscious shyness and concern about social evaluation and behavioral competence (e.g., performing well on the task, evaluation of performance by the experimenter) by early adolescence (Meyer 2017, Meyer et al. 2012, 2018b, Weinberg et al. 2016). We are continuing to test this possibility. In this way, ERPs may help to inform models related to the development of psychopathology by adding information beyond what might be reported by children or parents and beyond what can be observed behaviorally.

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Potential Mechanisms

Understanding laboratory-based manipulations of ERPs can help provide a context for gaining a better understanding of individual differences and psychopathology. For example, once an ERP correlate of a psychological disorder or individual difference has been identified, researchers can make new inroads by examining how that ERP is impacted by manipulations in the lab that may mimic factors in the environment and whether lab-based manipulations might alter individual differences.

We have repeatedly shown that the ERN is sensitive to the relative importance of errors: In the laboratory, we can potentiate the ERN through task instructions and manipulations that draw attention to performance accuracy and make errors more salient (Grützmann et al. 2014, Hajcak et al. 2005). Indeed, we have argued that hyperactive ERNs in anxious and high-risk individuals reflect a kind of overvaluation of the importance of errors, such that errors are more salient than they should be for anxious and at-risk individuals (Hajcak 2012, Proudfit et al. 2013, Weinberg et al. 2012b, 2016). Consistent with this possibility, Endrass and colleagues (2010) found in a group of healthy individuals the expected increase in ERN amplitude when errors were punished; however, in participants with OCD, the ERN was insensitive to the punishment manipulation. Moreover, group-related ERN differences were found only in the standard (i.e., nonpunished) condition; these data suggest that patients with OCD who have a large ERN may not be able to modulate error processing based on changing situational demands (Endrass et al. 2010).

Along similar lines, we have shown that the ERN can be increased in the lab by using a loud noise or shock as punishment for error commission, and that these effects persist after punishment is removed (Meyer & Gawlowska 2017, Riesel et al. 2012). We have used these punishment-related effects to develop and test a learning-based model of ERNs and anxiety. Specifically, we hypothesized that parenting styles characterized by criticality or low warmth may shape the ERN in offspring during early childhood. Critical or punitive parents tend to punish children's mistakes more intensely and more frequently (Robinson et al. 2001), which could result in an increased ERN. Consistent with this possibility, we found that punitive parenting styles are related to an increased ERN in young children (Meyer et al. 2015b) and that the ERN mediates the relationship between critical parenting and anxiety disorders in children. These effects were found when using observational or self-report measure of parenting (Meyer et al. 2015b), and they have been replicated in children as young as 4 years old (Brooker & Buss 2014).

These findings suggest that one mechanism whereby parenting impacts anxious outcomes in children is by potentiating children's neural response to their mistakes (i.e., by increasing the ERN). We recently extended these findings and have linked this process to a genetic polymorphism related to fear learning (Meyer et al. 2018a). Children with the met allele of the *BDNF* genotype are generally more impacted by parenting behavior (Ibarra et al. 2014) and display deficits in extinction learning (Johnson & Casey 2015). We conceptualize critical parenting in the context of fear learning, such that children associate making mistakes with punishment (i.e., parental criticism), and the increased ERN as reflecting a potentiated conditioned response. Consistent with this possibility, we found that critical parenting predicted an increased ERN in offspring, but only among children who carried the *BDNF* met allele (Meyer et al. 2018a). In this way, ERPs may be leveraged to characterize complex mechanisms involving the genes and environmental factors that underlie the development of psychopathology.

Insights and Issues

ERPs can be used to study normative development as well as early emerging individual differences and psychopathology (Meyer 2017); indeed, understanding normative developmental changes in ERPs is particularly important in terms of clinically relevant studies. For instance, interpreting differences in the ERN in relation to anxiety or risk is made more challenging against a backdrop of developmental changes in the ERN. Clinically meaningful studies will need to address further questions that concern both development and individual differences, including examining when ERPs are most predictive of outcomes and change. Along similar lines, and related to the next section, is the question, are ERPs more malleable at certain ages? And does it matter when you attempt to alter the ERN? Another possibility is that developmental changes in ERPs might be better predictors than single ERP measurements. That is, individual differences in developmental increases or decreases in ERPs over time might be as important as the size of the ERP at a single point in time. These topics can be addressed only through empirical studies, and many more longitudinal studies with large sample sizes are needed to begin to address the complex issues that arise at the intersection of development and individual differences.

We have provided some evidence regarding how ERPs could be informative for, and integrated into, developmental models of psychopathology—that is, how ERPs can provide valuable information that self-report and observational methods cannot. As one example, ERN data suggest that the same behaviorally inhibited individuals are characterized by a decreased ERN at age 6 and an increased ERN at age 9 (Meyer et al. 2018b); these data certainly suggest important neurodevelopmental changes over time as a function of early temperament, and they raise important questions for future research: What processes are increasing or changing that would explain a shift from a decreased to an increased ERN over time? We have suggested that this change tracks the development of specific anxious phenotypes (i.e., self-conscious concerns, the transition from external to internal sources of anxiety), although future work will be needed to further explore this and other possibilities.

Along similar lines, we have situated ERPs within broader psychological theories to explore potential mechanisms regarding when and how an increased ERN might develop. Specifically, we have linked laboratory-based ERN studies on punishment to the impact of punitive parenting styles on an offspring's ERN (Meyer 2016, 2017; Meyer et al. 2015b, 2018a). Thus, we view parenting as a specific vehicle whereby the ERN is shaped through learning-related mechanisms (i.e., associative conditioning and punishment). Moreover, our data suggest that the impact of parenting on an offspring's ERN may mediate the association between harsh parenting and anxious outcomes (Meyer et al. 2015b). This work indicates that the ERN may be a mechanism

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linking parenting behavior to psychopathology outcomes. We are examining whether parent-focused treatments that decrease harsh and critical parenting can alter the ERN in offspring.

ERPs: TREATMENT-RELATED RESEARCH

Pre- to Posttreatment Designs

If ERPs relate both to continuous and dichotomous clinical variables and can be used to predict changes in clinical outcomes, a natural question is whether treatments can normalize hyperactive ERPs and whether ERPs can predict the degree of treatment response (i.e., whether they differ by responder status). To answer these questions, treatment outcome research could include ERP measures both at pre- and posttreatment assessments. In this type of design, ERP measures are included just as one would include measures of symptoms.

Several studies have examined the effect of typical anxiety treatments (i.e., CBT or SSRIs, or both) on the ERN using pre- to posttreatment designs. In the first study in a pediatric sample, we found increased ERNs in youths with OCD both before and after successful CBT (Hajcak et al. 2008). This effect was subsequently replicated in a much larger and more heterogeneous sample (Ladouceur et al. 2018). Neither study found that changes in ERNs related to changes in symptoms; neither found that ERNs predicted treatment response. Kujawa and colleagues (2016) similarly found that adolescents with SAD were characterized by a larger ERN both before and after treatment with either CBT or an SSRI and that ERNs did not predict the response to treatment. Consistent findings have also been replicated in adults with OCD (Riesel et al. 2015): OCD was characterized by an increased ERN both before and after therapy; symptom changes were uncorrelated with changes in ERNs; and ERNs did not differentiate treatment responders from nonresponders. Another study similarly found no treatment-related changes in ERNs following CBT in anxious adults, although SSRIs appeared to increase the ERN, and a higher pretreatment ERN predicted greater changes in a fear-oriented symptom measure among individuals who received CBT (Gorka et al. 2018). Since this was the first study to find an association between the ERN and treatment response, studies will be needed to further examine the ERN as a predictor of treatment outcome. One prospective study in cocaine-dependent patients found that a reduced ERN at the beginning of cocaine detoxification predicted relapse at 3-month follow-up (Marhe et al. 2013). Future studies are needed to determine whether ERNs might relate to relapse following treatment for other conditions.

The evidence suggests that typical treatments for anxiety do not normalize an increased ERN. One possibility is that the ERN is related to the risk for anxiety but not the expression of an anxious phenotype: In this case, treatment-related effects on the ERN would not be expected unless treatments alter underlying risk processes that are reflected in the ERN. Another possibility is that more focused and novel interventions may yet reduce both the ERN and anxiety. In light of the fact that 40% of patients either drop out prematurely or do not respond to anxiety treatments (Roy-Byrne 2015), it is desirable to develop innovative treatments as add-ons or even alternative interventions for those patients with treatment-resistant anxiety. One possibility is that ERPs could be used to guide the development of more tailored and novel interventions, a possibility we consider in more detail in the next section.

Novel Targets for Interventions and Manipulations

Rather than attempting to determine whether the full course of a treatment can alter an ERP, another strategy is to first examine whether an intervention can impact an ERP of interest within

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a single experimental session. Consistent with this tactic, several labs have begun to examine whether it is possible to alter the ERN during a single session even among anxious individuals. For instance, we found that ERN amplitudes were markedly decreased in patients with OCD under dual-task conditions (Klawohn et al. 2016). Performing a secondary dual task resulted in a reduced ERN, and this reduction was larger in patients with OCD than in the group of healthy participants; moreover, under dual-task conditions, the ERNs in patients with OCD did not differ from those in controls (Klawohn et al. 2016). These data demonstrate that increased ERNs in clinical anxiety can be normalized, at least temporarily.

A number of other brief interventions in the lab have similarly been shown to reduce the ERN. For example, we have now shown in two studies that a single session of attention bias modification (ABM) appears to reduce the ERN (Nelson et al. 2015), even relative to a control condition (Nelson et al. 2017). ABM is a computer-based cognitive training approach that has been shown to reduce attentional biases toward threat and reduce symptoms of anxiety (Hakamata et al. 2010), and our data suggest that ABM might work to decrease the ERN. We are examining the impact of multiple sessions of an adaptive ABM training in adolescents on ERN and the development of anxiety over a longer period of time.

Schroder and colleagues (2018) found that a single session of expressive writing, relative to a control condition that also involved writing, reduced ERN amplitudes among individuals who scored high in chronic worry. Insofar as expressive writing has been shown to reduce anxiety, this study suggests a possible intervention strategy for individuals with anxiety that is characterized by an increased ERN (Schroder et al. 2018). Finally, mindfulness-based approaches have also been shown to normalize ERNs among clinically depressed individuals whose depression is characterized by a blunted ERN, indicating a potential intervention route for individuals with a reduced ERN (Barnhofer et al. 2017).

All of the studies described above have leveraged existing interventions in an effort to change the ERN. That is, the ERN was a novel target for existing intervention strategies, often in the context of a single session. One of the most encouraging aspects of these studies is that they demonstrate that it is possible to impact ERPs such as the ERN, at least in the short term. Further, these studies suggest possible strategies that might be useful adjuncts to existing treatments for individuals with an increased ERN. Finally, these studies certainly set the stage for larger and longer-term assessments of whether the ERN can be modified and whether doing so impacts clinical outcomes and individual differences.

Targets for Novel Interventions

None of the interventions described above was developed specifically to target an increased ERN. Rather than focusing on existing treatments and trying to change a specific symptom or syndrome, it might be possible to develop truly novel interventions by targeting ERPs linked to psychopathology and risk. In our view, this is the most aspirational clinical use of ERPs. This is a similar concept to what the Biomarkers Definitions Working Group described as the use of a clinical end point (Biomark. Defin. Work. Group 2001). That is, a biomarker should be mechanistic, indexing a process closely related to the cause of an illness such that manipulations that affect the biomarker impact clinical outcomes.

The Biomarkers Definitions Working Group suggested that biomarkers as potential targets for treatment should be studied in animal models to aid the development of pharmacological interventions. For example, single-unit recording studies in monkeys have identified error-related ACC activity (Godlove et al. 2011, Ito et al. 2003), and intracortical field potentials in rodents have similarly identified ACC activation in response to errors (Narayanan et al. 2013). In rodent

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models, muscimol can temporally inactivate the ACC, which results in altered error-related ACC activation and behavioral changes (Narayanan et al. 2013). Future work might build on these findings to identify pharmacological interventions to reduce anxiety that alter ACC activation in animal models and then in humans. Determining whether a potential pharmacological agent alters the ERN might be informative in drug development.

It is also possible to leverage brain stimulation techniques and neurofeedback to develop interventions that would directly target ERPs. In the case of the ERN, Reinhart & Woodman (2014) demonstrated that they could increase and decrease the ERN in healthy individuals with transcranial direct current stimulation. Other brain stimulation techniques that rely on transcranial magnetic stimulation suggest alternative strategies for modulating discrete neural functions (Huang et al. 2005).

Biofeedback has a long history in clinical psychology, and studies suggest that EEG-based measures can be successfully used with neurofeedback training to improve symptoms (Micoulaud-Franchi et al. 2014). Indeed, recent studies on a potential brain–computer interface have leveraged ERPs to perform a variety of tasks, including spelling (Mak et al. 2011). An intriguing possibility is to use brain–computer interface programs to directly train individuals to reduce their ERN following errors. In this way, it may be possible to use ERP-based biofeedback to target potential mechanisms of risk.

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Insights and Issues

ERPs can be readily integrated into traditional treatment outcome studies because they can be examined both in relationship to clinical change and as pretreatment predictors of clinical change. If ERPs can predict treatment-related responses, they could then be used to identify those patients who might respond best to treatment (Burkhouse et al. 2016) or to help assign patients to specific treatments. ERPs could be used for determining what works best and for whom. If an ERP is mechanistic and indexes a process that is causally related to illness, then manipulations that affect the ERP should impact clinical outcomes.

Traditional CBT and SSRIs do not seem to impact the ERN, and the ERN does not appear to robustly predict treatment response to traditional CBT or SSRIs. Yet the ERN is a robust predictor of subsequent changes in symptoms and psychopathology, and a range of strategies appears to modulate the ERN, at least in the short term. To us, these data collectively suggest the need to test and develop novel interventions that are more focused on altering the ERN. To our knowledge, no intervention has been designed to directly target the ERN, and pharmacological studies have not routinely considered ERPs as potential targets. Moreover, brain stimulation and neurofeedback might provide additional and more direct methods of altering ERPs.

CONCLUSIONS

ERPs can be used as robust measures of individual differences that are related both to continuous measures and categorical diagnoses. Variability in ERPs can shed light on brain-based differences between apparently similar conditions, as well as neural similarities that cut across traditional diagnostic boundaries. Similar phenotypes can have opposing impacts on ERPs, suggesting there are fundamental distinctions between phenotypes that may traditionally be viewed as overlapping. ERPs can be studied in the context of risk through family history designs, and they appear to reflect both current psychopathology (and related traits) and genetic risk. In longitudinal studies, ERPs can predict disorders and can be combined with other measures to improve the prediction of outcomes: ERPs provide incremental predictive ability. Along similar lines, ERPs

can moderate responses to stressful events and developmental trajectories. ERPs can also inform developmental models of psychopathology and can be used to test specific mechanisms of risk. Treatment studies can include ERPs as correlates and predictors of change. ERPs might even be used to facilitate the development of novel treatment and intervention approaches. All of these are actualities that are evident in reviewing a relatively narrow body of research on the ERN and anxiety.

We have argued that ERPs likely relate to multiple phenotypes simultaneously. The ERN, for instance, appears to relate in opposite directions to positively correlated phenotypes (e.g., anxiety in one direction, depression and externalizing in another). This example demonstrates the inherent difficulty of interpreting a zero-order correlation between an ERP and a single measure of individual differences. If an ERP also relates to unexpressed risk, then this issue is complicated even further. These are additional reasons why we should be quite comfortable with reliable but relatively modest effect sizes in studies relating ERPs to other measures of individual difference. Even with relatively modest effect sizes, we can improve prediction by combining ERPs with other measures.

We have studied the ERN—using the same or similar task—for nearly 20 years. It has taken that long to do systematic research to suggest that ERNs can predict risk and are viable targets for intervention. The choice to continue to study the same ERP has been viewed in terms of poor innovation, and certainly there are ways in which we have been beating the same drum in slightly different ways. This approach contrasts with the potentially more exciting option of trying to develop novel tasks in the search for new dependent variables. However, we believe that the clinical utility of ERPs, and neuroscientific measures more broadly, will follow only from the kind of deep dive that involves pursuing robust effects systematically.

In **Figure 2**, we propose a road map for clinically meaningful ERP and neuroscientific research; it is meant to represent a blueprint for research into individual differences based on the work we described above on the ERN and anxiety. Of course, the first step is choosing an ERP of interest based on its neurocognitive function and relationship to psychological constructs of interest. We have argued that progress in clinical neuroscience is limited by the psychometric properties of neural measures (Hajcak et al. 2017); in **Figure 2**, evaluating psychometric properties is depicted as a step that precedes the examination of individual differences. If an ERP does not have adequate psychometrics (e.g., internal consistency), there is no point in examining its relationship to other measures of individual difference.

Assuming an ERP relates to individual differences robustly (i.e., across multiple studies), it is then possible to meaningfully ask whether the ERP relates to risk, whether it can predict changes in symptoms and diagnoses prospectively, and whether the ERP is impacted by treatments. It is also possible to develop and test potential mechanisms and novel interventions that target specific ERPs. Of course, ERPs can be useful in less direct ways: They can inform and test existing theory and can contribute to generating new psychological knowledge about the etiology and pathogenesis of a disorder, especially in terms of relevant neurocognitive functions and potential mechanisms.

This review was meant to focus on how ERPs might be used concretely to combat a growing mental health crisis and improve the prevention and treatment of suffering. Establishing that an ERP robustly relates to individual differences using both continuous and between-group designs is a necessary first step. Once this foundation is established, we would argue that ERPs have three clinically significant uses: as predictors of risk, as predictors of treatment change, and as targets for change (**Figure 2**). We note that a successful ERP predictor may not function well as a target for treatment; for instance, an ERP could be a nonmodifiable biomarker of risk. **Figure 2** also suggests that all of the work described above functions within a developmental context. The end goal is

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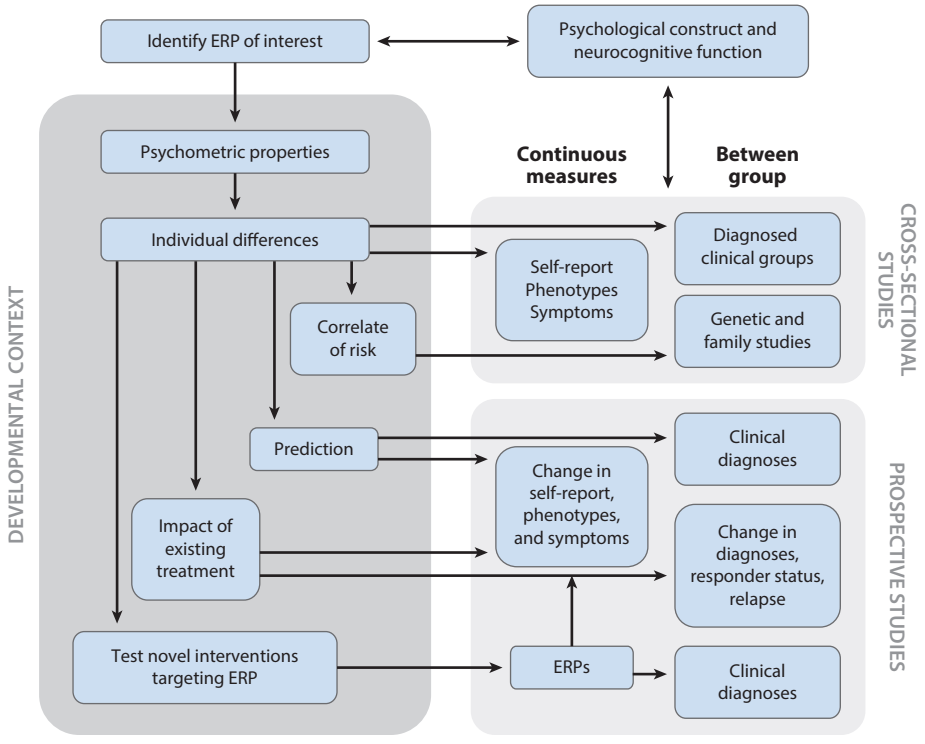

Figure 2

Blueprint for research into event-related potentials (ERPs) with clinical impact.

to have an ERP measure that can help guide individuals toward the most effective prevention or intervention approach.

Through systematic study, it is possible to determine exactly how an ERP might be used in clinically meaningful ways. We believe that the utility of ERPs in clinical psychology will come from the innovative use of well-replicated, but small, effects. ERPs will need to be combined with other measures and examined outside of university laboratories (e.g., in psychology clinics, doctor's offices, schools, homes). ERPs could be used to improve clinical decisions about prevention and intervention, although cost-effectiveness studies are needed to more fully evaluate this possibility. We imagine a future wherein ERPs could be more fully integrated into clinical practice (e.g., as an adjunct diagnostic and prognostic tool) and where novel interventions aim to alter these neural biomarkers of risk.

SUMMARY POINTS

1. Event-related potentials (ERPs) are robust and direct neural measures with good psychometric properties that can be used to study psychopathology and individual differences across development.
2. Specific ERPs likely relate to multiple phenotypes and disorders in ways that can clarify similarities and distinctions between disorders and traits.

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3. ERPs can be studied in relation to risk, using both family study and prospective designs; ERPs can prospectively predict the onset of new disorders even when accounting for other known risk factors, and they can similarly moderate the impact of other risk factors and stressors.
4. ERPs can be both heritable and impacted by environmental experiences that shape neural activity and risk for psychopathology.
5. ERPs can be used to develop and test models and mechanisms of risk, including developmental models of psychopathology.
6. ERPs can be used to predict responses to treatments, and they may be viable targets for the development of novel treatments.

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DISCLOSURE STATEMENT

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