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The error-related negativity (ERN) and psychopathology: Toward an Endophenotype

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Abstract

The ERN is a negative deflection in the event-related potential that peaks approximately 50 ms after the commission of an error. The ERN is thought to reflect early error-processing activity of the anterior cingulate cortex (ACC). First, we review current functional, neurobiological, and developmental data on the ERN. Next, the ERN is discussed in terms of three psychiatric disorders characterized by abnormal response monitoring: anxiety disorders, depression, and substance abuse. These data indicate that increased and decreased error-related brain activity is associated with the internalizing and externalizing dimensions of psychopathology, respectively. Recent data further suggest that abnormal error-processing indexed by the ERN indexes trait- but not state-related symptoms, especially related to anxiety. Overall, these data point to utility of ERN in studying risk for psychiatric disorders, and are discussed in terms of the endophenotype construct.

Research has begun to identify risk factors for psychiatric disorders. For example, having a parent with the disorder is a significant risk factor for anxiety disorders (Beidel & Turner, 1997), depression (Downey & Coyne, 1990), and substance abuse (Hartman, Lessem, Hopfer, Crowley, & Stallings, 2006). Personality factors are also a strong predictor for developing psychiatric disorders. For example, individuals reporting high levels of negative affect and the related personality trait of neuroticism report more anxiety and depressive symptoms (Jylha & Isometsa, 2006) and are commonly diagnosed with anxiety disorders (Hettema, Prescott, & Kendler, 2004), and major depressive disorder (Brown, Chorpita, & Barlow, 1998; Schmitz, Kugler, & Rollnik, 2003). In contrast, novelty seeking is a personality trait that is characterized by impulsivity and sensation seeking, and is a significant predictor for developing substance use disorders (Sher, Bartholow, & Wood, 2000).

High heritability rates of these disorders suggest that genetics play an important role in their etiology (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Kendler, Gardner, Gatz, & Pedersen, 2007; Middeldorp, Cath, Van Dyck, & Boomsma, 2005). However, isolating genetic causes of these potentially heterogeneous and complex diseases had proved to be difficult (Chakravarti & Little, 2003; Lewis, 2002). Recently, there is increasing focus on identifying

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[2]Following the ERN, another ERP component occurs on error trials: the error positivity (Pe). The Pe follows the ERN as a positive deflection 200–400 msec after the commission of an error (Figure 1a; Falkenstein, Hoormann, Hohnsbein, & Kleinsorge, 2003; Nieuwenhuis et al., 2001; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005) and has a more posterior midline scalp distribution than the ERN (Figure 1c; Falkenstein et al., 2000). There are several theories as to what the Pe represents, but studies have not systematically evaluated the Pe, so it is difficult to identify its role in error processing (Overbeek et al., 2005). Therefore, this review will only focus on the ERN and will not discuss Pe findings.

neural and information-processing abnormalities that may place individuals at risk for developing psychopathology. One way to do this is by studying endophenotypes, which are unobservable characteristics that mediate the relationship between genes and a given behavioral phenotype (Gottesman & Gould, 2003). Insofar as endophenotypes are less complex and heterogeneous than the associated disorder, endophenotypes might be determined by fewer genes and be more amenable to study.

The present paper will focus on neural activity related to action monitoring that is measured with event-related potentials (ERPs)—in particular, brain activity that indexes the on-going monitoring of correct and incorrect behavior. This review will concentrate on error-related negativity (ERN), focusing on its neural correlates and functional significance. The ERN will then be discussed in relation to psychiatric disorders and related personality traits. These data suggest that increased action monitoring indexed by the ERN might serve as a putative risk factor for anxiety and depression, whereas reduced ERNs might relate more to substance abuse disorders. Finally, these data are discussed in terms of the endophenotype construct, and future directions for relevant research are discussed.

Response Monitoring

Response monitoring tasks

The present paper focuses on ERP data recorded during a number of different speeded response tasks, including the Erikson Flankers task, the Simon task, color Stroop task, and the Go/No-Go task. In the arrows version of the Erikson Flankers task, participants respond to the direction of a central arrowhead which is flanked by either compatible (e.g., < < < < <) or incompatible (e.g., < < > < <) arrowheads (Eriksen & Eriksen, 1974). Similarly, in the Simon task, participants respond to a red circle with their left index finger and to a blue circle with their right index finger (Simon, 1969). Stimuli are presented either to the right or to the left of the center fixation cross, leading to congruent (e.g., red circle on the left side) or incongruent (e.g., red circle on the right side) trials. In the color Stroop task, names of colors are presented on a screen and participants are asked to respond to the *color* of the word. On congruent trials, the color of the target word matches the word (i.e., the word “red” is presented in red font), on incongruent trials, the color of the target word does not match the word (i.e., the word “red” presented in green font); on neutral trials, the word does not map directly to either response (i.e., the word “blue” presented in red font). Finally, the Go/No-Go task requires participants to respond to a target (i.e., Go stimulus) and withhold their response to a non-target distracter (i.e., No-Go stimulus).

Participants typically perform between 500 – 1500 trials in these tasks in relatively rapid succession. In all of these tasks, errors are relatively rare and are characterized by fast reaction times compared to correct responses (Rabbitt, 1966). This suggests that errors are due to impulsive responding, prior to complete processing of the stimulus (Rabbitt & Vyas, 1981). Interestingly, reaction times on correct trials after errors are typically slower than the average reaction time on correct trials. It is thought that such post-error slowing occurs in order to increase the likelihood of a correct response on the subsequent trial (Hajcak, McDonald, & Simons, 2003b; Rabbitt, 1981).

Error-related negativity and related components

When participants make errors in these speeded response tasks, an ERP component, the error-related negativity (ERN)[1], presents as a negative deflection approximately 50–100 ms following the erroneous response (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991;W.J. Gehring, Goss, Coles, Meyer, & Donchin, 1993). Typical response-locked ERPs for error and correct trials are presented in Figure 1a. The ERN has been observed across tasks that employ

a variety of stimulus and response modalities (Bernstein, Scheffers, & Coles, 1995;Holroyd, Dien, & Coles, 1998;Van't Ent & Apkarian, 1999) and task difficulty (Band & Kok, 2000;Mathalon et al., 2003;Mathewson, Dywan, & Segalowitz, 2005;Moser, Hajcak, & Simons, 2005;Themanson, Hillman, & Curtin, 2006). The ERN is typically measured at midline frontal or central sites where the ERN is largest (i.e., FCz); Figure 1b presents the typical scalp distribution of the ERN. It is hypothesized that the anterior cingulate cortex (ACC) is the generator of the ERN as evidenced by studies using source localization (Dehaene, Posner, & Tucker, 1994;Holroyd et al., 1998;van Veen & Carter, 2002), magnetoencephalography (W. H. Miltner et al., 2003), and intracerebral recording (Brazdil, Roman, Daniel, & Rektor, 2005). Additional confirmation of the relationship between the ERN and the ACC stems from human lesions studies showing that patients with ACC lesions have diminished ERNs (Stemmer, Segalowitz, Witzke, & Schonle, 2004) and from single-unit studies that show increased error potentials in the anterior cingulate cortex in monkeys (Gemba, Sasaki, & Brooks, 1986;Ito, Stuphorn, Brown, & Schall, 2003).

Interestingly, a small ERN-like component is sometimes evident on correct response trials (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Ford, 1999; Gehring & Knight, 2000; Scheffers & Coles, 2000; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). Because of its similarity to the ERN, this component has been referred to as the correct response negativity (CRN; Ford, 1999). Authors have suggested that CRN reflects a response comparison process (Falkenstein et al., 2000; Vidal et al., 2000), an emotional reaction (Luu, Collins, & Tucker, 2000), uncertainty of a correct response (Coles, Scheffers, & Holroyd, 2001; Pailing, Segalowitz, Dywan, & Davies, 2002), or coactivation of correct and incorrect responses (Luu et al., 2000; Scheffers, Coles, Bernstein, Gehring, & Donchin, 1996; Vidal et al., 2000).

Studies have consistently found that the ERN amplitude is larger when subjects make fewer errors (Amodio, Jost, Master, & Yee, 2007; Amodio, Master, Yee, & Taylor, 2007; Gehring et al., 1993; Hajcak et al., 2003b). Infrequent errors might make error commission especially significant, thus altering the amplitude of error signaling. Differences in subjects' performance may thus pose a confound when comparing ERP across groups with different error rates and reaction times (Hajcak, Vidal, & Simons, 2004; Yeung, 2004). That is, if a group of participants has larger ERNs than a control group, and commit fewer errors than the control group, it is possible that the between-group behavioral differences might account for variation in the ERN. However it is possible to control subjects' performance by providing feedback throughout the task (e.g., Hajcak & Foti, in press) or by only comparing subjects who are matched on performance (e.g., Tsai, Young, Hsieh, & Lee, 2005).

Trials with large ERN amplitudes have also been associated with increased post-error slowing (Debener et al., 2005; Gehring, Goss, Coles, Meyer, & Donchin, 1993). However, not all studies have replicated this pattern of results (Gehring & Fencsik, 2001; Scheffers, Humphrey, Stanny, Kramer, & Coles, 1999). Interestingly, studies show that it is possible for subjects to make errors that they are unaware of – and these unaware errors are associated with normal ERNs but reduced post-error slowing (Endrass, Reuter, & Kathmann, 2007; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). Therefore, post-error slowing appears to depend on error awareness, whereas the ERN does not.

[1]The focus of this review is the response related ERN, however, a similar component is observed following negative feedback (feedback ERN; W.H. Miltner, Braun, & Coles, 1997). Although this feedback-related component is similar to what is observed after a response error, there are significant differences between the two which have led some researchers to suggest that they are not the same component (W. J. Gehring & Willoughby, 2004; Hajcak, Moser, Holroyd, & Simons, 2006). Thus, this review will focus the psychophysiological response to errors or slips in fast reaction time tasks.

Functional Significance of the ERN

Several theories and computational models have been developed regarding the functional significance of the ERN. Some suggest that the ERN reflects the error-detection process (e.g., Falkenstein et al., 1991; Falkenstein et al., 2000; Nieuwenhuis et al., 2001; Scheffers et al., 1996), an error signal at the remedial action system (e.g., Holroyd & Coles, 2002), the conflict-detection process (e.g., Yeung, Cohen, & Botvinick, 2004), or a more emotionally- or motivationally-relevant response to errors (Bush, Luu, & Posner, 2000; Gehring & Willoughby, 2002; Pailing et al., 2002).

Mismatch Theory

According to the early mismatch theory, the ERN represents the detection of a mismatch between the representations of the actual and intended response (Bernstein et al., 1995; Coles et al., 2001; Falkenstein et al., 1991). Thus, ERN amplitude should be directly related to the degree of mismatch between the correct and actual response. Indeed, studies confirm that subjects have larger ERNs when the error response and the correct response are more dissimilar (Bernstein et al., 1995; Falkenstein, Hohnsbein, & Hoormann, 1995; Scheffers et al., 1996). This mismatch should also be larger when subjects are more certain of their errors. In fact, studies have shown that the ERN amplitude is increased when subjects are sure that they made an error, regardless of whether or not they actually make a mistake (Scheffers & Coles, 2000).

Reinforcement and Learning-based Theories

One of the more prominent computational models, based in part on the mismatch theory, is the reinforcement learning theory of the ERN (RL-ERN; Holroyd & Coles, 2002). According to the RL-ERN, the basal ganglia monitor information from both the environment (external) and self-generated actions (internal), and evaluate on-going events based on learned expectations (Holroyd & Coles, 2002). The RL-ERN is rooted in non-human animal work indicating that the basal ganglia induce an increase or decrease in phasic midbrain dopamine (DA) activity, when events are better or worse than expected, respectively (for review see Barto, 1995; Houk, Adams, & Barto, 1995; Schultz, 2002). The RL-ERN theory proposes that the ERN is the result of disinhibition of the ACC by DA neurons signaling events as worse than anticipated. From this perspective, error signals are important for learning because they are used to predict future rewards and non-rewards and to modify ongoing behavior (Barto, 1995; Montague, Dayan, & Sejnowski, 1996; Schultz, 2002).

Consistent with the RL-ERN's hypothesized role of DA in the generation of the ERN, administration of the DA agonist D-amphetamine leads to an increase in the ERN amplitude (de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004), whereas the administration of the DA antagonist haloperidol leads to a decrease in the ERN amplitude (de Bruijn, Sabbe, Hulstijn, Ruigt, & Verkes, 2006; Zirnheld et al., 2004). Demonstrating the specificity of DA neurotransmitter levels on the ERN, one study found that the selective serotonin reuptake inhibitor paroxetine had no effect on ERN amplitude (de Bruijn et al., 2006).

It is likely that changes in baseline DA levels are important for understanding the effects of dopaminergic agents on the ERN. This has been proposed in a new computational model, which builds upon the RL-ERN model, and states that *basal* DA levels can have a significant effect on reinforcement learning due to possible range restrictions on *phasic* DA bursts (Frank, 2005). For example, individuals with Parkinson's disease who are being treated with DA agonists may have elevated tonic DA levels that prevent effective phasic dips, which could hinder negative reinforcement learning. Since these phasic dips characterize the ERN signal, the ERN amplitude would be diminished in Parkinson's disease patients, which is consistent

with the literature (Falkenstein, Hielscher et al., 2001; Ito & Kitagawa, 2006; Stemmer, Segalowitz, Dywan, Panisset, & Melmed, 2007).

Conflict Monitoring Theory

Both the mismatch theory and the RL-ERN theory provide significant insight into the function of the ERN; however, in the context of these theories, it is unclear why an error occurs in the first place, especially if the correct representation is present at the time of the error (cf. Yeung et al., 2004). Another computational model, the conflict monitoring theory, addresses this concern by focusing on *conflict* detection rather than error detection, per se. The conflict monitoring theory is based on the idea that the role of the ACC is to monitor conflict during response selection and that errors are simply a specific example of response conflict that occurs between an erroneous and error-correcting response (Yeung et al., 2004). Specifically, both error and correct response representations are dynamically activated as a result of continued stimulus processing; on error trials, an error is therefore followed by an error-correcting response, which elicits conflict between the error and the error-correcting correct response (Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988; Rabbitt, 1981; Yeung et al., 2004). From this point of view, errors are simply trials on which response conflict crosses some threshold. The conflict monitoring theory identifies the ACC as the neural seat of conflict monitoring. In support of this, neuroimaging studies show that the ACC is activate not only following errors, but also on correct trials that are incongruent and elicited high response conflict (Bench et al., 1993; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Carter et al., 1998; Carter et al., 2000; MacDonald, Cohen, Stenger, & Carter, 2000; Pardo, Pardo, Janer, & Raichle, 1990).

A number of investigators has also compared the ERN to a negative deflection in the *stimulus*-locked ERP: the N2 peaks between 200–400 msec after stimulus presentation, and thus generally occurs prior to the execution of a response. It is most pronounced on trials with high response conflict, and is evident in the incongruent minus congruent stimulus-locked difference waveform on correct trials. For example, in the Flankers task, high response conflict occurs when the flanking arrows are in the opposite direction as the center arrow (< < > < <). The N2 is thought to reflect the coactivation of the correct and incorrect response on correct trials (Falkenstein, Hoormann, & Hohnsbein, 1999; Yeung et al., 2004). Some source localization studies show that the N2 and the ERN have similar scalp topographies and a common neural source (caudal ACC), but they occur at different times relative to the response. That is, N2 occurs *prior to correct* responses and the ERN occurs *following erroneous* responses (Carter et al., 1998; van Veen & Carter, 2002; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001; van Veen, Holroyd, Cohen, Stenger, & Carter, 2004; Yeung et al., 2004). Collectively, these results raise the possibility that ERN-like activity might reflect both error-detection and the more general detection of response conflict on correct trials.

The original version of the conflict monitoring theory does not account for the CRN. In the conflict monitoring theory, increased conflict should occur prior to the response on correct trials but after the response on error trials (Yeung et al., 2004). However, it has recently been suggested that conflict might occur at multiple levels. Van Veen and Carter (2005) studied both stimulus and response conflict while participants performed a Stroop task. They found that although the ACC was active during both forms of conflict, specific regions of the ACC differed, which suggests that different forms of conflict processing occur in parallel. Therefore, CRN might be related to conflict at the response level. In fact, work by Bartholow and colleagues indicates that incompatible trials yield a larger CRN amplitude than compatible trials (Bartholow et al., 2005). Thus, the relatively new suggestion that conflict may influence ERPs at multiple levels of stimulus and response processing appears to allow for the possibility that the ERN and CRN, as well as the stimulus-locked N2, reflect conflict monitoring.

Motivational Significance Theory

A major shortcoming of existing computational models is that they do not account for motivational and individual differences. Errors are motivationally salient events that prompt psychophysiological changes that include skin conductance and heart rate deceleration (Hajcak et al., 2003b; Hajcak, McDonald, & Simons, 2004). Although these peripheral responses are consistent with both a defensive and orienting response, a recent study from our lab found that the defensive startle reflex was larger following errors than correct responses (Hajcak & Foti, 2008). In fact, Hajcak and Foti found that the ERN predicted degree to which the startle reflex was potentiated after errors. Collectively, these data suggest that the ERN might reflect error-detection that is utilized for motivational ends. Thus, amplitude of the ERN might relate to the *significance* of an error. This possibility was first suggested by Gehring and colleagues (1993) who reported that the amplitude of the ERN was larger when an error was made when participants were told to be more accurate, whereas the ERN was smaller when participants were told to respond faster. Therefore, by emphasizing accuracy, the authors could have made errors more salient which in turn could have made them more important or negative (Hajcak, Moser, Yeung, & Simons, 2005).

Additional studies suggest a role for motivational significance in modulating amplitude of the ERN. One study used two different paradigms to assess motivational effects on ERN amplitude: a Flankers task in which subjects could either win or lose 5 or 100 points, and a Flankers task administered under conditions of performance evaluation (Hajcak et al., 2005). In both of these experiments, errors associated with a motivationally significant context (i.e., losing 100 points or being evaluated) coincided with a larger ERN amplitude compared to the other conditions. More recent studies replicate these results and indicate that more valuable or significant errors result in a larger ERN (Chiu & Deldin, 2007; Kim, Iwaki, Uno, & Fujita, 2005).

The motivational significance view of the ERN is often discussed in terms of affective processes as well. Vidal and colleagues (2000) suggested that the ERN may be influenced by an individual's emotional reaction to errors. Interestingly, one study found that motivational significance was only influential in the magnitude of the ERN in individuals with certain personality traits (Pailing & Segalowitz, 2004). For example, individuals rating high on conscientiousness and low on neuroticism had smaller motivation-related effects on ERN amplitude.

Error-Monitoring and Individual Differences

Error monitoring and age

A number of studies has examined developmental changes in the ERN. In a large study that examined the ERN in children from age 7 to 18, Davies and colleagues did not find an observable ERN in children younger than 12 (Davies, Segalowitz, & Gavin, 2004a, 2004b). Contrary to this, other studies have reported ERNs in children ranging in age from 7 to 11 (Hajcak, Franklin, Foa, & Simons, 2007; Kim, Iwaki, Imashioya, Uno, & Fujita, 2007; Wiersema, van der Meere, & Roeyers, 2007). Preliminary data from our lab provides evidence that ERNs are even present in children as young as 5, provided simple tasks are employed (Torpey, Hajcak, & Klein, 2007). In regard to developmental trends in ERN amplitude, several researchers have reported smaller ERN amplitudes in children (ages 7–18) compared to adults (Kim et al., 2007; Wiersema et al., 2007). The ERN has also been correlated with age, suggesting that it increases with development (Hajcak et al., 2007).

One study showed that adolescents (ages 13 – 14) have comparable ERN amplitudes to adults (ages 23 – 24; Wiersema et al., 2007). On the other hand, Ladouceur and colleagues (2004) found that the ERN amplitude was larger in late adolescents (ages 14 – 17) compared to early adolescents (ages 9 – 14). Overall, these findings suggest that changes in ERN amplitude reflect

developmental changes in the brain, possibly reflecting the continued maturation of the medial prefrontal cortex, with increasing ERN amplitude through childhood and adolescence that plateaus in late adolescents or early adulthood (Davies et al., 2004a, 2004b)

In older adults (ranging between ages 54 – 85), studies have consistently found decreased ERN amplitude when compared to young adults (ranging between ages 18–28; Band & Kok, 2000; Falkenstein, Hoormann, & Hohnsbein, 2001; Mathalon et al., 2003; Mathewson et al., 2005; Nieuwenhuis et al., 2002; Themanson et al., 2006). It is important to note, though, that some of these findings may be confounded by behavioral differences, such as decreased accuracy in older adult groups (Band & Kok, 2000; Mathewson et al., 2005; Nieuwenhuis et al., 2002).

One of the initial studies suggested that decreased ERN amplitude in older adults may result from a decreased ability to detect errors (Band & Kok, 2000). Although this may be true in more difficult tasks, it is unclear why the ERN would be reduced when subjects perform relatively simple tasks. Another suggestion is that decreased ERN amplitude is due to diminished dopaminergic function that occurs with normal aging (Nieuwenhuis et al., 2002). Likewise, decreased ERN amplitude in children may be due to neurodevelopment of medial prefrontal cortex (Stuss, 1992) and dopaminergic neurons that continues until early adulthood (Levitt, 2003; Segawa, 2000). In support of this view, the scalp distribution of the ERN in 5 – 6 year olds appears to be more posterior compared to adults (Torpey et al., 2007), suggesting some anteriorization over the course of development. Therefore, it is possible that developmental changes in DA and the prefrontal cortex across the life span are at the root of developmental changes in ERN amplitude.

Error-monitoring and psychopathology

ERN and anxiety—Consistent with the notion that obsessive-compulsive disorder might be characterized by abnormal action monitoring (Pitman, 1987), Gehring and colleagues first reported that patients with OCD had increased ERNs compared to age-matched controls (Gehring, Himle, & Nisenson, 2000). This pattern of results has now been replicated (Johannes et al., 2001; Ruchsow, Gron et al., 2005), and consistent results have also been reported in children with both generalized anxiety disorder (GAD) and OCD (Hajcak et al., 2007; Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006). Additionally, several fMRI studies have confirmed the findings of increased error-related brain activity in OCD patients (Fitzgerald et al., 2005; Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005; Ursu, Stenger, Shear, Jones, & Carter, 2003). One study found increased ACC activity in both error and correct trials in OCD patients, signifying an overall hyperactivity in the ACC during response monitoring (Ursu et al., 2003); similar results were reported in an ERP study that showed both an increased ERN and CRN in high-OC subjects (Hajcak & Simons, 2002).

Hajcak and colleagues (2007) demonstrated that ERN amplitude does not change after successful treatment in pediatric OCD. These findings have since been replicated in an additional report (Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2007). Another study that examined state-related changes in anxiety with spider phobic individuals found that the ERN amplitude did not change during symptom provocation with the presence of a tarantula (Moser et al., 2005). Combined, these studies suggest that the ERN is not affected by state-related changes in anxious symptoms.

In support of this possibility, several studies have examined the ERN with respect to personality traits that are closely related to pathological anxiety. Two studies have found that subjects scoring high on negative affect have significantly larger ERN amplitudes compared to subjects scoring low on negative affect (Hajcak, McDonald et al., 2004; Luu et al., 2000). Additionally, pathological worry has been associated with increased ERN amplitude (Hajcak, McDonald, &

Simons, 2003a). An fMRI study similarly found increased ACC activity on error trials in individuals with high trait anxiety (Paulus, Feinstein, Simmons, & Stein, 2004).

Other evidence suggests that negative affect is strongly related to individual differences in punishment sensitivity (Carver & White, 1994; Watson, Wiese, Validya, & Tellegen, 1999). Two studies have examined behavioral inhibition system (BIS) and behavioral activation system (BAS) scores relative to ERN amplitude (Amodio, Master et al., 2007; Boksem, Tops, Wester, Meijman, & Lorist, 2006). BIS and BAS scores are thought to represent punishment sensitivity and reward seeking, respectively (Carver & White, 1994; Gray, 1972, 1981). Consistent with the notion that errors are aversive, both Boksem and colleagues (2006) and Amodio and colleagues (2007) found that subjects with high BIS scores also had larger ERNs. BIS and BAS traits relate to biases towards reactive and proactive control respectively (Boksem et al., 2006; Braver, Gray, & Burgess, 2007; Gray & Braver, 2002), and may also relate to learning style. For example, another study found that participants who learned by avoiding negative events (i.e., reactive control) had larger ERNs than individuals who learned from positive events (i.e., proactive control; Frank, Woroch, & Curran, 2005).

ERN and depression—Depressed individuals exhibit increased sensitivity to mistakes and negative feedback (Elliott, Sahakian, Michael, Paykel, & Dolan, 1998; Steffens, Wagner, Levy, Horn, & Krishnan, 2001). Individuals endorsing depressive symptoms were shown to have decreased accuracy after incorrect compared to correct trials, which is evidence of poor performance adjustments following errors (Holmes & Pizzagalli, 2007; Pizzagalli, Peccoralo, Davidson, & Cohen, 2006). A negatively biased view of the environment is also thought to be a strong factor in the development of depression (Beck, 1967; Leppanen, 2006). Depressed individuals accurately judged the number of error responses they made, but underestimated the number of correct responses in a working memory task (Dunn, Dalgleish, Lawrence, & Ogilvie, 2007).

In line with these negative processing biases, depressed individuals also exhibit abnormal error-related activity. For example, while performing a Stroop task, depressed subjects had greater ERN amplitude compared to controls (Holmes & Pizzagalli, 2008). Additionally, while performing a Flanker's task, depressed subjects had greater ERN amplitude in neutral and punishment conditions compared to controls, but no difference in ERN amplitude during a reward condition which supports the notion that depressed individuals are especially sensitive to punishment (Chiu & Deldin, 2007). An fMRI study likewise found increased rostral ACC activity in depressed patients compared to controls during error trials (Steele, Meyer, & Ebmeier, 2004).

Conceptually, both anxiety and depression appear to be characterized by an increased sensitivity to committing errors – consistent with studies that report an increased ERN in relation to anxiety and depression. In fact, Hajcak and colleagues (2004) argued that abnormal ERN amplitude may not be specific to pathological conditions of depression or pathological anxiety, but rather reflect an underlying characteristic that is central to both of these disorders – negative affect (cf., Luu et al., 2000). However, an alternative possibility is that the ERN is increased in all forms of psychopathology. Next, we review evidence that the ERN shows an *opposite* pattern of effects in disorders characterized by insensitivity to errors and other forms of punishment - namely substance abuse.

ERN and substance abuse—In the only study to date that has examined the ERN in relation to substance abuse, Franken and colleagues found that cocaine dependent patients had decreased ERN amplitudes compared to a control group (Franken, van Strien, Franzek, & van de Wetering, 2007). The relation between substances of abuse and error monitoring has also has also been studied by acutely administering alcohol to healthy volunteers. Both low and

moderate doses of alcohol decrease ERN amplitude in healthy individuals (Easdon, Izenberg, Armilio, Yu, & Alain, 2005; Ridderinkhof et al., 2002). However, no studies to date have looked at state-related ERN changes in substance abusers.

Imaging studies, however, support the notion that substance abusers, regardless of what drugs they abuse, exhibit reduced error-related ACC activity. For example studies have found decreased error-related ACC activity in individuals who use marijuana (Gruber & Yurgelun-Todd, 2005), opiates (Forman et al., 2004), cocaine (Goldstein et al., 2007; Kaufman, Ross, Stein, & Garavan, 2003) and methamphetamine (London et al., 2005). Overall, these results suggest that individuals with substance abuse may have a decrement in error-processing, although more ERP studies are required to examine this with specific regard to the ERN.

A hallmark personality characteristic in substance abuse is impulsivity (Moeller et al., 2001) which is often characterized by enhanced sensitivity to reward and reduced sensitivity to punishment (Corr, 2002; Monterosso & Ainslie, 1999). Similarly, those at risk for developing substance abuse disorders are more sensitive to rewards than punishment (Finn, Kessler, & Hussong, 1994) and are particularly insensitive to long-term negative consequences which are usually dismissed in favor of short-term rewards (Grant, Contoreggi, & London, 2000; Petry, Bickel, & Arnett, 1998).

Consistent with the suggestion that impulsivity is related to increased sensitivity to reward and decreased sensitivity to punishment (Corr, 2002; Monterosso & Ainslie, 1999), studies show that individuals who score high on impulsivity scales have decreased ERN amplitudes in response to errors (Potts, George, Martin, & Barratt, 2006; Ruchsow, Spitzer, Gron, Grothe, & Kiefer, 2005). Other studies have found similar results using more indirect measures of impulsivity. For example, individuals characterized as externalizing often have impulsive control problems (Krueger, Hicks, Patrick, & Carlson, 2002; Krueger, Markon, Patrick, & Iacono, 2005). As expected, high externalizing individuals also had smaller ERN amplitudes (Hall, Bernat, & Patrick, 2007).

Overall then, increased ERNs appear specific to disorders such as anxiety and depression, whereas decreased ERNs have been reported in individuals with substance abuse and impulsive personality characteristics. This pattern of increased and decreased ERNs fit well within contemporary models of psychopathology that posit two higher-order factors of psychopathology (Krueger, 1999): specifically, internalizing and externalizing disorders might be characterized by hyperactive and hypoactive error-processing, respectively, as indexed by the ERN.

Summary

ERN is a reliable index of error-processing, evident just 50 ms after individuals make mistakes; the available evidence indicates that the ERN is generated in the ACC, and likely reflects dopaminergic activity related to the on-going evaluation of errors and response conflict (Holroyd & Coles, 2002; Yeung et al., 2004). There is increasing evidence that ERN also relates to motivational and affective variables, and might be tied to neural systems that support defensive behaviors and avoidance learning (Frank et al., 2005; Hajcak & Foti, 2008).

Individuals with internalizing disorders, characterized by increased sensitivity to errors (i.e., anxiety and depression), are characterized by increased ERNs. Similar results are found in personality traits closely related to internalizing forms of psychopathology: individuals that score high in negative affect, anxiety, worry, and behavioral inhibition all have increased ERN amplitudes (e.g., Amodio, Master et al., 2007; Boksem et al., 2006; Hajcak et al., 2003a; Hajcak, McDonald et al., 2004). Moreover, it appears that state-related changes in anxiety do not have a corresponding influence on the ERN (Hajcak et al., 2007; Moser et al., 2005).

Collectively, these results support the notion that abnormalities of the ERN are related to stable characteristics related to internalizing disorders.

Externalizing disorders, on the other hand, are characterized by impulsivity and behaviors that go against societal norms (Krueger, Caspi, Moffitt, & Silva, 1998; Krueger, Markon, Patrick, Benning, & Kramer, 2007). Individuals with substance abuse problems are often typified by impulsive behaviors (Moeller et al., 2001) and often making decisions that result in short-term rewards at the expense of long-term negative consequences (Grant et al., 2000; Petry et al., 1998). Psychophysiological and imaging studies confirm that individuals with substance abuse disorders have decreased ERN amplitude (Franken et al., 2007) and error-related brain activation (i.e., Goldstein et al., 2007), indicating that these individuals are less sensitive to errors.

Personality traits, such as impulsivity, that are associated with externalizing are characterized by a similar reduction in the ERN (e.g., Potts et al., 2006); along similar lines, individuals who are characterized by insensitivity to punishment have reduced ERNs in the context of punishment but not reward (Dikman & Allen, 2000). These results support the notion that a reduced ERN appears related to the externalizing dimension of personality and psychopathology.

Conclusions and Future Directions

We have previously proposed that the ERN might be a useful endophenotype for internalizing disorders (Hajcak, Franklin, Foa, & Simons, 2007). In particular, the ERN might reflect information-processing abnormalities that mediate the pathway between genetic predisposition and disease states (Gottesmann & Gould 2003). Gottesmann and Gould (2003) highlighted several characteristics of endophenotypes. First, an endophenotype should be associated with a disease. Several studies have shown that increased error-related brain activity characterizes patients with anxious (Gehring, Himle, & Nisenson, 2000; Hajcak et al., 2003a; Hajcak, McDonald et al., 2004; Hajcak & Simons, 2002; Ruchsow, Spitzer et al., 2005) and depressive symptoms (Chiu & Deldin, 2007). Additionally, an endophenotype should be state-independent. This has been verified in anxiety disorders, with studies showing no change in ERN amplitude during symptom provocation (Moser et al., 2005) or after successful treatment (Hajcak et al., 2007; Ladouceur et al., 2007). To our knowledge, though, there have been no research studies to date that have looked at state changes in symptoms of depressed patients. Endophenotypes must also be heritable. Preliminary studies reported by Anohkin, Golosheykin, and Myers (2008) indicate that error-related brain activity is heritable, with estimates in the range of .30 to .50. Also, endophenotypes should be more evident in unaffected first-degree family members of patients compared to first-degree family members of non-patients. This has not been assessed, as of yet, and is certainly an important topic for future study.

Of course, the present review highlights the possibility that a *reduced* ERN might also relate to the externalizing dimension of personality and psychopathology; however, further research needs to be done to confirm and extend these findings. Future studies might clarify other remaining issues. For example, more studies are needed to assess changes in ERN amplitude after successful treatment in order to tease apart state and trait influences on the ERN. Some studies have already suggested that trait-related differences in anxiety relate to an increased ERN, whereas no studies have similarly examined the impact of state-related depressive changes on the ERN. Finally, longitudinal studies beginning in childhood are necessary to examine the ERN in children prior to the development of psychiatric disorders to establish a time-line for when differences in ERN amplitude begin to signify risk.

Although many psychiatric disorders can be categorized into the internalizing-externalizing dimension, psychotic disorders such as schizophrenia do not fit well within this model – and questions remains as to whether or not psychotic disorders represent an entirely unique dimension (see Krueger & Tackett, 2003). Interestingly, the literature suggests that individuals with schizophrenia represent a unique dimension: in contrast with the internalizing and externalizing dimensions characterized by increased and decreased error-sensitivity, respectively, schizophrenia is characterized by a general inability to self-monitor (Malenka, Angel, Hampton, & Berger, 1982; Stirling, Hellewell, & Quraishi, 1998).

Although most studies indicate that individuals with schizophrenia have smaller ERN amplitudes (Alain, McNeely, He, Christensen, & West, 2002; Bates, Kiehl, Laurens, & Liddle, 2002; Bates, Liddle, Kiehl, & Ngan, 2004; Kim et al., 2006; Morris, Heerey, Gold, & Holroyd, 2007; Morris, Yee, & Nuechterlein, 2006), some evidence suggests that individuals with schizophrenia also have larger CRN amplitudes that are comparable in magnitude to their ERNs (Mathalon et al., 2002; Morris et al., 2006). These findings are similar to what is seen in individuals with prefrontal cortex lesions who have no difference between their ERN and CRN amplitudes (Gehring & Knight, 2000). The similarities between schizophrenia and prefrontal cortex lesion patients are not surprising as deficits in the prefrontal cortex are thought to contribute to the etiology of schizophrenia (Galderisi et al., 2007; Zhou et al., 2007). One difference between these two groups is that PFC lesion patients have normal ERN amplitudes, whereas schizophrenia patients have smaller ERN amplitudes. During errors of commission, schizophrenic patients had a decreased hemodynamic response in the ACC (Carter, MacDonald, Ross, & Stenger, 2001) and more specifically in the rostral ACC (Laurens, Ngan, Bates, Kiehl, & Liddle, 2003). Additionally, studies suggest that schizophrenia is also characterized by decreased structure and function of the ACC (Zetzsche et al., 2007). Future studies should investigate both the ERN and the CRN in schizophrenia to determine whether changes in both of these components represent a general inability of individuals with schizophrenia to self-monitor. It is of interest to note that there is an abundant literature on the P300 component in schizophrenia which suggests that deficits in attention may impact task performance and related psychophysiological measures (see Ford, 1999 for a review). Thus, ERN findings may result from a more general deficit found in schizophrenia rather than being specific to response monitoring.

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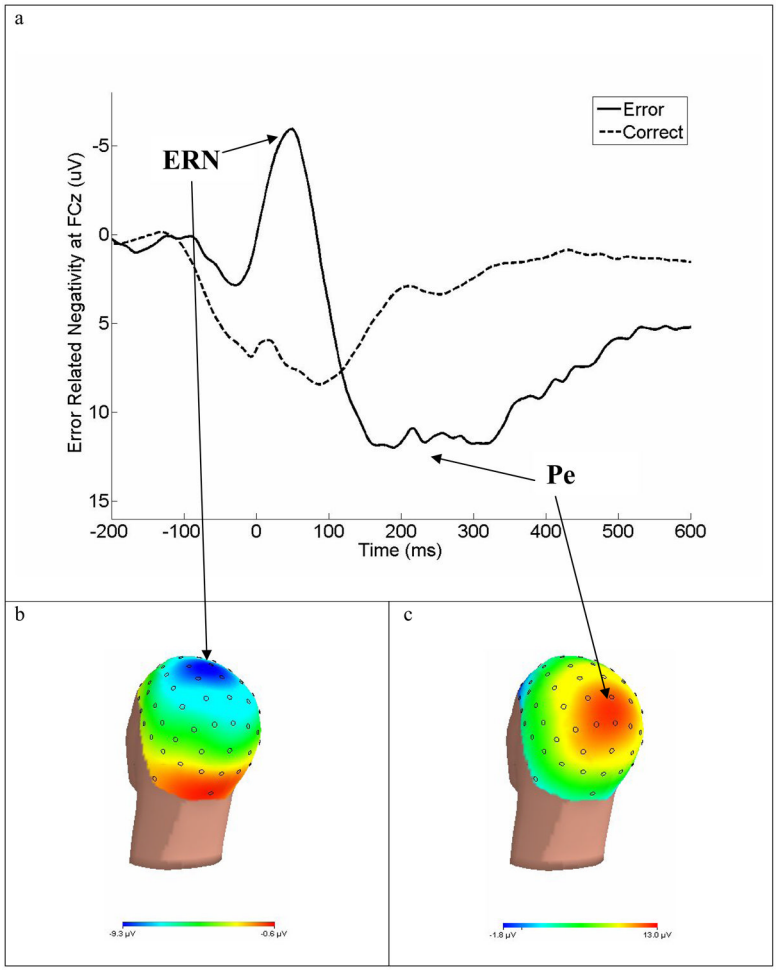

Figure 1.

The response locked ERPs for error and correct trials at FCz, where the ERN was maximal (a). The response onset occurred at 0 msec and negative is plotted up. Scalp topography of error-related brain activity from 0 to 100 msec post-response (b). Scalp topography of error positivity from 200 to 400 msec post-response (c).