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COMMENTARY

The NIMH Research Domain Criteria initiative and error-related brain activity

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Abstract

Research on the neural response to errors has an important role in the Research Domain Criteria (RDoC) project, since it is likely to link psychopathology to the dysfunction of neural systems underlying basic behavioral functions, with the error-related negativity (ERN) appearing as a unit of measurement in three RDoC domains. A recent report builds on previous research by examining the ERN as a measure of the sustained threat construct and providing evidence that the ERN may reflect sensitivity more specifically to endogenous threat. Data from 515 adolescent females indicate that the ERN was enlarged primarily in older adolescents with self-reported checking behaviors, although it was blunted in adolescents with depressive symptoms regardless of age. Potential future studies for replicating and extending the research on the ERN and obsessive-compulsive (OC) behaviors are discussed, including studies that more fully characterize OC symptom dimensions, studies that integrate other measures of error-related brain activity and use computational modeling, studies that combine longitudinal, family, and molecular genetic measures, and interventional studies that specifically modulate error-related brain activity in individuals with OC behaviors.

Descriptors: Adolescents, Anxiety, Performance monitoring, ERPs

The article by **Kozak and Cuthbert (2016)** provides an incisive and succinct historical summary of the shortcomings of the categorical approach to psychiatric diagnosis in the United States. Although Robins and Guze (1970) explicitly stated that disorders failing validation by their approach require reconceptualization, that process was followed only to a limited extent after the introduction of the DSM-III. As a template for biopsychopathology research, the Research Domain Criteria (RDoC) initiative promotes research on a neural circuit or system that implements the psychological function of a valid behavioral construct associated with a clinical psychiatric phenomenon. As part of the effort, **Kozak and Cuthbert (2016)** state that "considerable research is needed to create behavioral and self-report scales that reflect the constructs they purport to measure," indicating that numerous studies will be required to define a set of behaviors and symptoms associated with a particular neural circuit across the life span.

Research on the neural response to errors fits well in the RDoC project, since it is likely to link psychopathology to the dysfunction of neural systems underlying basic behavioral functions. The ability to detect and respond to errors is crucial to adapting in a changing environment, giving it a central role in monitoring goal-directed behavior (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The error-related negativity (ERN) or error negativity (Ne) is a negative deflection in the event-related potential that peaks within 100 ms after an incorrect response, which can be evoked by errors committed outside of conscious awareness (Gehring, Liu, Orr, & Carp, 2012). The ERN appears as a unit of measurement in three RDoC domains: cognitive systems (cognitive control: performance monitoring), negative valence systems (sustained threat), and positive valence systems (reward learning). While it may be possible to separate cognitive from affective processes, the placement of the ERN in three RDoC domains indicates the ERN reflects variance in each of these domains and functionally integrates both cognitive and motivational factors (Shankman & Gorka, 2015). The identification of behaviors or symptoms associated with an enlarged ERN is consistent with the RDoC mission, since "it invites concentration on narrowly defined complaints or impairment that might be more tractable than heterogeneous symptom clusters" (**Kozak & Cuthbert, 2016**).

The report by **Weinberg and colleagues (2016)** builds on previous research by their group by examining the ERN as a measure of the sustained threat construct and providing evidence that the ERN may reflect sensitivity more specifically to endogenous threat. Data from 515 adolescent females indicate the ERN was enlarged primarily in older adolescents with self-reported checking behaviors, although it was blunted in adolescents with depressive

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symptoms regardless of age. Using the Inventory of Depression and Anxiety Symptoms, checking behaviors were assessed with three items, whereas ordering and cleaning behaviors were assessed with five and seven items, respectively. The specific relationship between the ERN and checking behaviors requires replication in other samples using instruments that more thoroughly assess obsessive-compulsive (OC) symptoms and other recurrent and persistent thoughts that are experienced as intrusive, poorly controlled, and threatening. If the ERN is particularly sensitive to endogenous threat, it may be associated with measures of obsessions involving violent images, fears of acting on unwanted impulses (e.g., stealing, blurting out obscenities, or committing incest, bestiality, suicide, or homicide), and excessive worries about sacrilege, blasphemy, or scrupulosity. It is also unknown whether the ERN may have had equally strong correlations with more general parent-report and self-report measures such as the obsessive-compulsive scale and anxiety problems scale from the Child Behavior Checklist and Youth Self-Report in large adolescent samples (Nelson et al., 2001; Van Grootheest et al., 2008).

Since the study by **Weinberg and colleagues (2016)** is novel in its RDoC design and large sample size, it is difficult to compare it to previous studies of the ERN in either children or adults. In a study from another group comparing adults with obsessive-compulsive disorder (OCD) and matched healthy controls using categorical diagnoses, brain activity during performance monitoring was increased in OCD patients compared to controls (Riesel, Kathmann, & Endrass, 2014). Amplitudes of the ERN and correct-related negativity (CRN) along with delta and theta power were used to quantify performance monitoring, and a composite score was derived from these measures using factor analysis. Performance monitoring was uncorrelated in OCD patients with their lifetime OC symptom dimension scores, but was correlated in patients with a current measure of superstitious fears and rituals, counting compulsions, mental rituals, and measures other than checking to prevent harm or terrible consequences. In contrast to the study from **Weinberg and colleagues (2016)**, there was no correlation between performance monitoring and doubt/checking behaviors.

Since the ERN has been consistently enlarged in studies of OCD and appears to be a trait marker or endophenotype for the disorder that usually has no correlations with OC symptom severity (Carrasco et al., 2013; Hajcak, Franklin, Foa, & Simons, 2008; Reisel, Endrass, Kaufmann, & Kaufmann, 2010), it may be more difficult to demonstrate a relationship between the ERN and specific OC behaviors in a clinical sample with narrowly defined diagnoses than in a clinical or community sample with minimal diagnostic exclusions. The results from the study by Weinberg and colleagues indicate that a sample with a continuous distribution of checking behaviors may have the ability to detect a relationship between performance monitoring and specific OC behaviors that may be missed in more traditional studies comparing only patients with OCD and controls with no psychiatric diagnoses.

It is important to note that theories of the ERN continue to evolve on many fronts, including the computational role of the ERN in behavior, its neural localization, and the precise characterization and measurement of the electrophysiological event that we measure at the scalp (see Gehring et al., 2012, for a review). This growing understanding of the ERN must proceed in parallel with refinements in the characterization of the three RDoC constructs associated with it. For example, the use of delta and theta power in the study by Riesel and colleagues (2014) provides an interesting method for corroborating the potential relationship between brain activity during performance monitoring and checking behaviors across disorders. It is presently unclear whether traditional ERP component amplitude measures provide a more complete picture of the neural activity underlying the ERN than do measures based on time-frequency analysis, but future development of the ERN as an endophenotype would do well to consider the utility and theoretical basis for different measurement strategies, because missing significant aspects of the ERN as a neural phenomenon would be as limiting as not measuring significant OC symptoms.

A continuing conflict in the literature linking performance monitoring with OC behaviors is the role of the CRN. It makes intuitive folk-psychological sense for OCD to be associated with exaggerated error detection activity when behaviors are objectively correct (as when an individual actually turns off a stove but retains a disturbing sense of doubt). However, observations of enhancement in the CRN have been inconsistent (e.g., compare Endrass, Klawohn, Schuster, & Kathmann, 2008, with Gehring, Himle, & Nisenson, 2000), and so far theories and empirical studies have had little to say on this discrepancy. Interestingly, although the Weinberg et al. study focused on the delta ERN, their waveforms show changes in the amplitude of the CRN between the various panels of their Figure 2 that could contribute to the observed relationships between OC symptoms and the delta ERN. In particular, the observation that checking behaviors interact with age in influencing the delta ERN raises the possibility that the CRN varies in a similar fashion. These possibilities point to the potential for enriching the RDoC approach with a neurodevelopmental perspective (Casey, Oliveri, & Insel, 2014): the large number of participants of varying ages will allow investigators to work out subtle relationships between physiology and behavior—such as the relative contribution of correct- and error-trial activity and how they change with development—that have eluded investigators working within a more traditional framework.

Finally, computational modeling has had tremendous value in advancing cognitive theories of the ERN (Holroyd & Coles, 2002; Yeung, Botvinick, & Cohen, 2004), with some models even providing quantitative predictions of the changes in neural activity over time (e.g., Yeung et al., 2004). Computational modeling has been less influential, however, in research that attempts to relate the ERN to clinical constructs. This disconnect is as much a reflection of the need for extending cognitive models to the clinical realm as it is for clinical theories to incorporate computational modeling. In work extending the **Weinberg et al. (2016)** study, computational models may provide a more precise picture of the range of internal events that could be classified as sustained threat and delineate the process by which detection of such events results in a computation that enhances the scalp-recorded ERN. Another appeal of such models is that they may help connect behavioral and physiological observations with genetic variation, because the structural and neurochemical differences that arise in part from genetic differences may be amenable to extensions of the computational models that have thus far been useful in understanding the ERN.

Even if other studies determine that the ERN has a specific relationship with checking behaviors, taboo obsessions, or a range of superstitious fears, counting compulsions, mental rituals, and measures other than checking to prevent harm, the causal connection between error-related brain activity and specific OC symptoms will remain to be established. Here again, computational models that show how the activity manifests in overt behavior may be useful in this endeavor. Moreover, as with the guidelines from Robins and Guze (1970), follow-up studies of individuals like those in the **Weinberg et al. (2016)** study may be done to assess the outcome

of individuals with an enlarged ERN and specific OC behaviors. Similarly, family studies may be done to determine whether an enlarged ERN cosegregates with specific OC behaviors in the relatives of individuals with an enlarged ERN and those behaviors. However, it will still be necessary for ongoing genetic studies to determine whether variation in the ERN mediates the genetic risk for specific OC behaviors rather than indicating risk through pleiotropic effects by sharing a set of genes with the clinical phenotype (Walters & Owen, 2007). If the ERN or other measures of error-related brain activity are demonstrated to mediate the risk for specific OC behaviors, it may be possible to use the information to develop diagnostic or therapeutic applications. In particular, interventional studies will be necessary to develop psychological or biological treatments that modulate error-related brain activity and to determine whether specific OC behaviors can be reduced or eliminated with them.

References

Carrasco, M., Harbin, S. M., Nienhuis, J. K., Fitzgerald, K. D., Gehring, W. J., & Hanna, G. L. (2013). Increased error-related brain activity in youth with obsessive-compulsive disorder and unaffected siblings. *Depression and Anxiety*, *30*, 39–46. doi: 10.1002/da.22035

Casey, B. J., Oliveri, M. E., & Insel, T. (2014). A neurodevelopmental perspective on the research domain criteria (RDoC) framework. *Biological Psychiatry*, *76*, 350–353. doi: 10.1016/j.biopsych.2014.01.006

Endrass, T., Klawohn, J., Schuster, F., & Kathmann, N. (2008). Overactive performance monitoring in obsessive-compulsive disorder: ERP evidence from correct and erroneous reactions. *Neuropsychologia*, *46*, 1877–1887. doi: 10.1016/j.neuropsychologia.2007.12.001

Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components, II: Error processing in choice reaction tasks. *Electroencephalography and Clinical Neurophysiology*, *78*, 447–455. doi: 10.1016/0013-4694(91) 90062-9

Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science*, *4*, 385–390. doi: 10.1111/j.1467-9280.1993.tb00586.x

Gehring, W. J., Himle, J. A., & Nisenson, L. G. (2000). Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science*, *11*, 1–6. doi: 10.1111/1467-9280.00206

Gehring, W. J., Liu, Y., Orr, J. M., & Carp, J. (2012). The error-related negativity (ERN/Ne). In S. K. Luck & E. Kappenman (Eds.), *Oxford handbook of event-related potential components*. New York, NY: Oxford University Press.

Hajcak, G., Franklin, M. E., Foa, E. B., & Simons, R. F. (2008). Increased error-related brain activity in pediatric OCD before and after treatment. *American Journal of Psychiatry*, *165*, 116–123. doi: 10.1176/appi.ajp.2007.07010143

Holroyd, C. B., & Coles, M. G. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, *109*, 679–709. doi: 10.1037/0033-295X.109.4.679

Kozak, M. J. & Cuthbert, B. N. (2016). The NIMH Research Domain Criteria initiative: Background, issues, and pragmatics. *Psychophysiology*, *53*, 286–297.

Nelson, E. C., Hanna, G. L., Hudziak, J. J., Botteron, K. N., Heath, A. C., & Todd, R. D. (2001). Obsessive-compulsive scale of the Child Behavior Checklist: Specificity, sensitivity, and predictive power. *Pediatrics 108*, e14. doi: 10.1542/peds.108.1.e14

Riesel, A., Endrass, T., Kaufmann, C., & Kathmann, N. (2010). Overactive error-related brain activity as a candidate endophenotype for obsessive-compulsive disorder: Evidence from unaffected first-degree relatives. *American Journal of Psychiatry*, *168*, 317–324. doi: 10.1176/appi.ajp.2010.10030416

Riesel, A., Kathmann, N., & Endrass, T. (2014). Overactive performance monitoring in obsessive-compulsive disorder is independent of symptom expression. *European Archives of Psychiatry and Clinical Neuroscience*, *264*, 707–717. doi: 10.1007/s00406-014-0499-3

Robins, E., & Guze, S. B. (1970). Establishment of diagnostic validity in psychiatric illness: Its application to schizophrenia. *American Journal of Psychiatry*, *166*, 1–7. doi: 10.1176/ajp.126.7.983

Shankman, S. A. & Gorka, S. M. (2015). Psychopathology research in the RDoC era: Unanswered questions and the importance of the psychophysiological unit of analysis. *International Journal of Psychophysiology*. Advance online publication. doi: 10.1016/j.ijpsycho.2015.01.001

Van Grootheest, D. S., Bartels, M., Van Beijsterveldt, C. E. M., Cath, D. C., Beekman A. T., Hudziak J. J., & Boomsma D. I. (2008). Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at ages 12, 14, and 16. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 1182–1188. doi: 10.1097/CHI.0b013e3181825abd

Walters, J. T. R., & Owen, M. J. (2007). Endophenotypes in psychiatric genetics. *Molecular Psychiatry*, *12*, 886–890. doi: 10.1038/sj.mp.4002068

Weinberg, A., Meyer, A., Hale-Rude, E., Perlman, G., Kotov, R., Klein D. N., & Proudfit, G. (2016). Error-related negativity (ERN) and sustained threat: Conceptual framework and empirical evaluation in an adolescent sample. *Psychophysiology*, *53*, 372–385.

Yeung, N., Botvinick, M. M., & Cohen, J. D. (2004). The neural basis of error detection: Conflict monitoring and the error-related negativity. *Psychological Review*, *111*, 931–959. doi: 10.1037/0033-295X.111.4.931