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Using Event-Related Potentials and Startle to Evaluate Time Course in Anxiety and Depression

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Abstract

NIMH's Research Domain Criteria (RDoC) is a research framework designed towards understanding psychopathology as abnormalities of dimensional neurobehavioral constructs rather than in terms of DSM defined categories. RDoC constructs within the negative valence domain are particularly relevant for understanding anxiety and depressive disorders, which are pervasive, debilitating, and characterized by negative processing bias. One important direction for RDoC research is investigating processes and parameters related to the time course (or chronometry) of negative valenced constructs. Two reliable methods for assessing chronometry are event-related potentials (ERPs) and startle blink. In this qualitative review, we examine ERP and startle studies of individuals with anxiety, depression, or individuals vulnerable to affective disorders. The aim of the review is to highlight how these methods can inform the role of chronometry in the spectrum of anxiety and depression. ERP studies examining different chronometry facets of negative valenced responses have shown that transdiagnostic groups of individuals with internalizing psychopathologies exhibit abnormalities at early stages of processing. Startle reactivity studies have robustly differentiated fear-based disorders (e.g. panic disorder, social phobia) from other anxiety disorders (e.g., generalized anxiety disorder) and have also shown that different internalizing phenotypes exhibit different patterns of habituation. Findings lend support to the value of ERP and startle measures in identifying groups that cut across conventional classification systems. We also highlight methodological issues that can aid in the validity and reproducibility of ERP and startle findings and, ultimately, in the goal of developing more precise models of anxiety and depression.

Keywords

Research Domain Criteria; chronometry; threat; affective disorders; startle blink; ERP

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Introduction

Anxiety and depressive disorders are prevalent illnesses that are leading causes of mortality, disability, and lost productivity worldwide (1). The cost to the individual and society cannot be overstated, yet, our understanding of anxiety and depression has been hindered by the current categorical diagnostic system. While applicable to all psychiatric illnesses, anxiety and depression exemplify the shortcomings of our classification system, which largely emphasizes observed behaviors (2), rather than mechanistic or etiological factors.

Another issue with the current classification system is the extensive comorbidity. For example, most individuals with major depression (MDD) will have experienced a concurrent anxiety disorder and vice versa (3). Relatedly, there is substantial symptomatic heterogeneity within each disorder as two individuals with the same disorder can have very different symptom presentations (4). Furthermore, the categorical approach does not take into account the severity of the symptomatology, including the clinical relevance of sub-threshold symptomatology (5) and is less reliable and valid than a dimensional approach (2, 6).

In response to these limitations and against a backdrop of neurobiological discoveries signifying psychiatric disorders as ‘brain disorders’, the NIMH’s Research Domain Criteria (RDoC) initiative aims to develop a more precise taxonomy by linking neurobiological measures to clinical behaviors that cut across traditional diagnostic categories (7, 8). Briefly, the RDoC framework encompasses multiple units of analysis (e.g., circuits, physiology, behavior) to measure constructs and processes (i.e., domains) implicated in functioning and behavior. Since psychobiological functions tend to be continuous in nature with no clear cutpoint(s) differentiating normal from abnormal, RDoC emphasizes a dimensional construct-guided framework in conceptualizing and defining psychopathology.

RDoC constructs within the negative system domain, a domain which is primarily responsible for responses to aversive situations, such as fear, anxiety, and loss, are particularly relevant for depressive and anxiety disorders (although these disorders relate to constructs within other domains as well (9)). Toward this effort, electroencephalography (EEG) and electromyographic (EMG) measures have the potential to make important contributions to understanding these constructs and the RDoC mission in general. These low-cost, portable, non-invasive technologies permit the collection of large samples, which are necessary in capturing meaningful individual differences. Furthermore, advances in analytic methods and technology are increasing the units of measure that can be extracted from these modalities. For example, improvement in signal processing and visualization have increased the ability to evaluate the spatial resolution of the EEG signal (10, 11). Additionally, integrating complementary psychophysiological and neuroimaging modalities to simultaneously collect EEG, EMG, and functional magnetic resonance imaging (12, 13) has wide-ranging applications (although these multimodal approaches are not without important technical challenges (14, 15)).

It has long been viewed that psychobiological measures are well-suited to inform dimensional conceptualizations of anxiety and depression. We focus the present review on how parameters of the *time course* of negative valence constructs measured with event-

related potentials (ERPs) and EMG startle blink could help elucidate key processes in these disorders. This review also discusses methodological factors to consider when implementing these psychobiological measures.

Negative Valence Chronometry

One important direction for RDoC research pertains to the time course (or chronometry (16, 17)) of responses. Chronometry refers to a series of processes and parameters reflecting the temporal dynamics of responding and is noted (either implicitly or explicitly) in numerous parts of the RDoC matrix. For example, three of the negative valence system constructs within the RDoC matrix¹ relate to different chronometric aspects of threat responding - sustained, acute, and potential threat. However, other aspects of chronometry are important to negative valence responding in depression and anxiety and ERP and EMG startle studies have long emphasized these in past research. Below, we review several key findings that have used these methodologies in studying the role of negative valenced constructs in anxiety and/or depression.

ERPs and Negative Valence Chronometry

Longstanding cognitive models propose that biases to negatively valenced stimuli play a critical role in the development and maintenance of anxiety and depression by forming, or reinforcing, maladaptive views of the self and others (e.g., schemas) (19, 20). Numerous behavioral studies have shown that anxiety is associated with 'early' automatic attention to signals of threat (e.g., fearful faces; threatening images) and depression is associated with 'late' strategic bias to signals of loss or failure (e.g., sad faces; mood-congruent words) (21–23). Yet, behavioral indices of bias (e.g. response time in probe detection or emotional Stroop tasks) have poor internal consistency and unacceptable test-retest reliability (24–27). Moreover, the demarcation of early and late processing tends to be broadly defined (e.g., < than 500 vs. > 1,000 milliseconds) (22, 23, 28).

ERPs comprise time-locked EEG activity to sensory, cognitive, or motor events and have the requisite temporal resolution to probe the earliest stages of predominately sensory-driven information processing as well as subsequent transitions to higher-order cognitive functions (29). Broadly, numerous studies have shown that emotional stimuli (e.g., unpleasant/pleasant images) modulate ERPs that map onto 'cold' cognitive processes (e.g., attention, conflict monitoring/resolution) (29, 30). Early ERPs that relate to affective processes include P1 and P2, which peak around 80–100 milliseconds (ms) and 100–250 ms after stimulus onset, respectively (31–36), with early posterior negativity (EPN) starting about 150–200 ms after stimulus exposure. These ERPs, along with N2, which peaks about 250–350 ms after stimulus onset represent automatic visual attention to emotional stimuli (37–41) such that higher amplitude denotes greater attention (42, 43). The late positive complex (LPC), consisting of the P300 and late positive potential (LPP), begins around 300 ms and continues several hundred milliseconds thereafter reflecting higher-order stages of processing (38–41,

¹It is important to note that the RDoC matrix put forth by the NIMH is not designed to be a definitive nomenclature - either in terms of constructs or units of analysis (8, 18). Thus, studies should not be restricted to the specific aspects of chronometry that are present in the existing matrix on the RDoC website.

44) including expectation violations (45, 46) and elaborative processing of emotional content (44, 47).

Unlike behavioral indices of biases, ERPs possess moderate-to-strong internal consistency and test-retest reliability especially for ERP amplitudes (48–50) though the reliability of ERPs are affected by the number of trials collected (49). Overall, ERPs have adequate psychometric properties although further study is needed to evaluate factors that may impact reliability and validity, for example, participant characteristics (e.g., unselected samples vs. patients with affective disorders).

ERPs and depression and anxiety—As an extensive review of ERP findings in depression and anxiety is beyond the scope of this paper, we highlight several studies that illuminate the utility and importance of this unit of analysis in understanding affective chronometry. In addition to the temporal continuum that underlies ‘early’ to ‘late’ emotion-related functions, ERPs are sensitive to ‘negativity bias,’ or the tendency to preferentially attend to negative cues (51–53). This bias is captured by ERPs such as P1, P2, N2, and LPC (e.g., P3, LPP), which are amplified when exposed to negative stimuli (relative to positive or neutral stimuli) (54, 55) indicating that the prioritization of negative stimuli occurs at both automatic and strategic stages of information processing. Evidence of early negativity bias in depression include data showing higher ERP amplitudes (e.g., N1, P1, P2) to sad faces in depressed individuals relative to healthy controls (56, 57). In depressed adolescents, there is evidence of greater P1 and LPP responses to negative words (58) suggesting bias that begins in the early stages of processing in depression may continue into later cognitive stages (though see (59)).

Moreover, ERPs such as the LPP appear to distinguish anxiety from depression. In a study of patients with anxiety and depressive disorders, depression, but not anxiety, was associated with reduced LPP to positive and aversive images (60). Of note, the result was driven by individuals with early onset depression suggesting a subtype of depression accounted for LPP effects (60). Reports that adolescents with current or remitted MDD exhibit equivalent LPP responses to emotional stimuli (61) indicate a history of depression may modulate LPP as well. The effect of depression history is likely relevant for understanding the mixed LPP results observed for generalized anxiety disorder (GAD) with some studies showing elevated LPP and others showing reduced LPP response (62, 63). That is, individuals with GAD are likely to have a history of depression (64) and while GAD studies frequently exclude current depression, the impact of remitted depression has been neglected. Altogether, LPP may yield distinct neural signatures along the anxiety and depression spectrum though further research is necessary to elucidate the extent to which sources of heterogeneity interact with LPP.

In terms of chronometry, ERP findings are contrary to behavioral findings of bias (20–23) which indicate that emotional thresholds (16) early in the course of processing differentiates anxiety from depression. Also, attenuated emotional responsivity, especially at later stages of processing may be a marker of depression given blunted reactivity to negative stimuli is frequently observed in depression and individuals vulnerable to depression (65–67).

Collectively, ERPs appear to provide a more nuanced and comprehensive description of *when* and *what* biases are present in anxiety and depression. Additionally, later processing

windows may be especially sensitive in capturing subgroups that exhibit certain cognitive (e.g., concentration problems) or somatic (e.g., fatigue) symptomatology. Consequently, ERP-related parameters could also aid in the assessment of ‘recovery time’ – when an individual’s emotional response returns to homeostatic baseline (16).

What constitutes ‘negative’ is an important consideration in chronometry and the RDoC framework. By convention, negatively valenced stimuli such as threatening (e.g., fear, angry) and sad faces are used to study anxiety and depression, respectively. As noted above, anxiety is frequently characterized by excessive, rapid detection of threat (21–23), therefore, ERPs representing early threat perception should be associated with anxiety disorders. However, findings convey a more complex picture. For example, in two studies utilizing emotionally-valenced stimuli (e.g., threat, happy, neutral faces), socially anxious individuals exhibited larger P1 or P2 amplitudes than non-anxious individuals (68, 69) across facial expressions signifying initial hyper-vigilance to faces. Conversely, threat-specific disturbances may be detected later, beginning in the ‘middle’ phases of processing as evidenced by greater EPN amplitude to fearful faces in socially anxious participants relative to healthy controls (70). Broadly, findings are consistent with hybrid discrete-dimensional models of emotion where early stages of processing reflect coarse categorization of stimuli (e.g., salience of faces) and later stages involve higher-order processes (e.g., psychological significance of threat) (71, 72).

Another consideration when using ERPs to study affective chronometry constructs are non-emotional features; for instance, stimulus properties (e.g., luminance, complexity, spatial frequency, arousal) affect ERPs (73, 74). Arousal is especially pertinent in the study of internalizing conditions as hyperarousal is more strongly linked with anxiety than depression (75). Regarding time course, arousal-related positivity begins early (150–200 ms latency) reaching maximum effects at longer latencies (30). Thus, controlling for non-emotional stimulus characteristics such as arousal is essential when examining phenotypes within and across anxiety and depressive disorders.

Low-level stimulus features (e.g., luminance, spatial frequency) also influence ERPs to facial expressions (76). Faces are of particular interest across psychopathologies as most social interactions involve the ability to discern another’s emotions, intentions, and actions which are frequently conveyed by facial expressions. The N170 is specific to faces (77, 78) and represents one of several face processing stages that spans automatic and elaborative functions (79). Regarding stimulus characteristics, this ERP is sensitive to emotion content (e.g., angry, fearful, happy) (31, 80, 81) (though, see (41, 82)) as well as perceived arousal, regardless of face type (83). For example, in healthy participants the arousal associated with facial expressions modulates N170 to a greater extent than the emotions conveyed by expressions (anger, happy) (83). The N170 also appears to measure negative bias as studies have reported larger N170 amplitudes for sad (84) and angry faces (85) in depression and social anxiety, respectively. This disorder-specific interpretation, however, should be made cautiously as the studies used separate faces – threatening for anxiety and sad for depression. While this approach is efficient when evaluating the N170 in terms of a categorical classification system, valuable information is lost when restricting the breadth and intensity of negative expressions. In addition to expanding stimuli beyond threatening and sad faces,

expressions of negative moral judgment (e.g., contempt, disgust) (86, 87) have the potential to identify homogenous groups within and across diagnostic categories.

ERPs elicited by behaviors may also serve as biomarkers. Notably, error-related negativity (ERN) occurring about 50 ms after the commission of an error (88, 89) is commonly associated with anxiety (90, 91) whereas reward positivity (RewP), appearing approximately 250–350 ms following the receipt of reward (92), frequently corresponds with depression (e.g., blunted RewP) (93, 94). Yet, inconsistencies have been observed, for example, enhanced and blunted ERN has been shown in MDD (95–99). Mixed findings may pertain to comorbid anxiety, which has not been consistently considered across studies; also, while ERN reflects threat sensitivity (100), it likely encompasses other RDoC domains (e.g., cognitive control) (100). Furthermore, blunted RewP may not be unique to depression (e.g., attenuated RewP corresponds with high trait anxiety) (101); again, comorbidity may factor into mixed findings. Indeed, when evaluating RewP in a highly comorbid patient sample, reduced RewP was associated with affective distress/misery but not fear-based symptoms in patients with anxiety and/or depression (102). Altogether, increased understanding of processes that underlie domains and alternative taxonomies have the potential to enhance the ability of ERN and RewP to identify transdiagnostic phenotypes.

Summary and unanswered questions—ERPs provide a coarse-to-fine analysis of emotion processing. Additionally, anxiety and depression modulate ERPs to motivationally-relevant stimuli to varying degrees. Indeed, ERPs including ERN and RewP represent distinctive functions that have the potential to identify groups that cut across diagnostic boundaries as well as elucidate mechanisms that are not easily identified with other units of analysis. Nonetheless, more research is necessary. For example, studies have predominantly used stimuli prototypical of anxiety and depression, therefore, findings may not generalize to transdiagnostic processes. Also, it is unclear whether stimuli features beyond content (e.g., arousal) differentiate particular subgroups of individuals and if the psychometric properties of ERPs (48–50) extend to clinical populations, a fundamental step in determining the value of ERPs in anxiety and depression.

Another important area of research are methods to delineate the neuroanatomical underpinnings of ERPs. Although simultaneous EEG-MRI recordings are promising, for example, the N170 is preserved in fMRI and is highly reliable (103), the artifacts generated by MRI on EEG/ERP signals suggest on-going study is essential to ensure the integrity of neurophysiological measures during simultaneous recording (14, 15). Alternative approaches to improve the spatial resolution of ERPs include current source density (11, 104) and low resolution electromagnetic tomography (105). These techniques have been shown to explicate the spatial localization of neuroelectric activity in individuals vulnerable to internalizing psychopathologies (66, 106) and clinical populations (107, 108) and have good-to-excellent temporal reliability when certain criteria are met (e.g., minimum of 10 trials for analysis) (109, 110). Nevertheless, the accuracy of localization with these and other techniques is unclear and thus the ability of ERPs to yield a fine assessment of topographic activity is debated among experts (111). Lastly, since ERPs are based on averages of EEG activity, they do not capture the fast, dynamic activity associated with neural oscillations or resting-state networks (112). Accordingly, methods that quantify the dynamic properties of

functional connectivity networks measured with EEG (e.g., connectomics) constitute another ‘unit’ of measure that can be used in RDoC studies. Alternatively, dynamic activity of ERPs could be examined by averaging subsets of trials (e.g., every 6 of a particular trial type) to examine the time course of the ERPs over the course of a task. This would require, of course, knowledge of how many trials of a condition produce a reliable signal to know the minimum number of trials needed for these ‘mini-averages.’

Startle Blink and Negative Valence Chronometry

The startle reflex is an index of defensive responding to aversive stimuli (e.g., loud sound, shock) (113, 114) and is found in humans and non-human animals (115) making it suitable for translational research. The eyeblink reflex is an adaptive response to aversiveness and an electromyogram (EMG) of the orbicularis oculi muscle reliably captures the strength of the blink (114). Features that impact startle include the nature of a threat where imminent/predictable threat elicits phasic fear and unpredictable threat induces sustained fear (i.e., anxious apprehension) (116–119). Notably, the distinction between predictable and unpredictable threat is represented as “acute” and “potential” threat, respectively, in the negative valence domain of the RDoC matrix (120) and these constructs are well-supported with psychophysiological studies that have used the No Threat, Predictable Threat, Unpredictable Threat (NPU-threat) paradigm (117, 121).

The NPU-threat task consists of three within-subjects conditions: 1) no threat (participants are safe from aversive stimuli), 2) predictable threat (aversive stimuli are signaled by a brief cue), and 3) unpredictable threat (aversive stimuli are not signaled). Throughout the task, the startle blink reflex to probes (e.g., bursts of white noise) is recorded as an index of aversive responding. Accordingly, the predictable condition assesses acute threat and the unpredictable condition, potential threat. Regarding psychometric properties, both conditions are known to produce reliable startle potentiation in multiple studies (122, 123). One study showed that a reliable signal in non-clinical and clinical samples can be generated with as few as six startle responses per condition (123). In contrast, studies that have used affective pictures to emotionally modulate startle (not reviewed here) have reported more varied reliabilities (122, 124–126).

The distinction between acute and potential threat plays an important role in dimensional classification systems where internalizing disorders are grouped into higher-order factors of ‘fear’ and ‘distress-misery’ (127–130). In support, startle responses to potential but not acute threats have been shown to distinguish fear from distress-misery disorders (specifically, panic disorder from MDD) (131) (see also (132)). Moreover, Shankman and colleagues found that independent of anxiety symptoms, a heightened startle response to unpredictable threat (SUT) was associated with a family history of fear, but not distress-misery, disorders (133). Interestingly, these effects are not evident across all anxiety phenotypes, as we recently showed that a heightened SUT specifically characterizes those with fear-based disorders (e.g. panic disorder, phobias) but not distress-misery disorders (e.g., generalized anxiety disorder) (9).

One of the ways that startle studies can examine the chronometry of affective response is by examining aspects of the time course of startle over the course of an experiment. For

example, using growth curve modeling with each startle response modeled as an independent event, one can model both the slope of startle over the course of the experiment (reflecting the habituation of startle) and initial intercept (reflecting initial startle reactivity, see (134) for how growth curve modeling can be applied to psychophysiological studies broadly). Taking this approach, Gorka et al. (135) found that individuals with panic disorder (without depression), MDD (without panic disorder), and panic disorder with concurrent depression, demonstrated an initial heightened startle response to unpredictable threat relative to healthy controls suggesting that heightened startle reactivity was common to individuals with internalizing disorders relative to controls, but did not distinguish diagnostic groups. However, rate (i.e., slope) of habituation to unpredictable threat differentiated groups. Specifically, individuals with panic disorder, regardless of depression status, exhibited less of a decrease in startle response during unpredictable threat compared to individuals without panic symptoms. Conversely, depressed individuals (with or without panic disorder) showed greater reduction in startle magnitude to predictable threat relative to those without depression (135).

Startle has also been used to study the chronometry of negative valence by examining responses to pending versus more distal threats. Waters et al. (136) found that adolescents with primary fear conditions (specific phobia, social phobia) exhibited larger startle magnitude when threat was more distal compared to adolescents with distress disorders (depression, dysthymia, generalized anxiety disorder, posttraumatic stress disorder), but not when the threat was more pending. As adolescents with fear disorders also exhibited heightened startle magnitude across the safe condition, these results together suggest a pattern of hypervigilance to threat and an overgeneralization of defensive responding among individuals with fear-based conditions (136).

Summary and unanswered questions—Collectively, these studies demonstrate the effectiveness of startle eye-blink in identifying RDoC constructs and chronometric processes that distinguish fear from distress-misery disorders. The distinction between these types of disorders has been demonstrated by numerous factor analytic studies of the phenotypic structure (127, 130, 137) as well as genotypic structure of psychopathology (138, 139). Though fewer studies have attempted to identify mechanisms and processes that distinguish fear from distress-misery disorders, a recent review also found support for how startle can distinguish fear from distress-misery disorders (140), although considerable heterogeneity in defensive reactions was observed. Findings underscore the necessity of large samples and multiple units of analysis (140), including those involved in the chronometry of negative valence response, which appears to be an under-researched area of study.

Other aspects of chronometry

Besides the aspects and parameters of chronometry discussed above, there are numerous others that are likely important to negative valence responding in depression and anxiety. Indeed, one of the first parameters discussed by Davidson (16), who likely coined the term ‘affective chronometry,’ was ‘rise time to peak,’ a parameter reflecting how long it takes for an affective response to reach its peak intensity before dissipating. This variable is highlighted in the diagnostic criterion for a panic attack in the requirement that the attack

must reach its peak ‘within minutes’ (141). Rise time to peak is likely important for numerous negative valence responses but, interestingly, has not received as much attention in experimental neurophysiological studies (although one research group has begun to examine it using novel fMRI methods (142, 143)). Given the excellent temporal resolution offered by ERP and startle, measuring ‘time to peak’ is an important future direction for studies using these methodologies.

A second important parametric property is whether the time course of responding is linear or non-linear. A non-linear time course could take many forms. For example, if one is studying habituation, it would be important to test whether there potentially are curvilinear habituation patterns (144, 145). Another form of non-linear effects would be whether there are ‘tipping points.’ Tipping points refer to points on a continuum that mark meaningful transitions to more severe (or at least different) behaviors and have been identified as important factors in RDoC research (146, 147). As an example of a tipping point outside of ERP/startle research, Mitchell and colleagues (148) found that youth who experienced 7 or more non-victimization types of adversity had significantly higher depression than those with fewer than 7, thus, 7 childhood adversities marked the tipping point for depression. As ERPs and startle involve repeated responses and/or presentations of stimuli, it is possible that there is a ‘tipping point’ within a task (or perhaps a tipping point in how many times a person does a task) that distinguishes qualitatively different psychological states. To our knowledge, tipping points have never been examined in neurophysiological research but would be an important area of future research.

Conclusions

The RDoC initiative put forth by the NIMH is an exciting and novel approach towards conducting research on depression and anxiety disorders as it seeks to examine dimensional constructs rather than categorically defined psychopathologies. Constructs focusing on the time course, or *chronometry*, of negative valence responding are worthy of study and this review highlights the utility of ERP and startle biomarkers for this aim. Of course, a fundamental requirement in the development of biosignatures is sufficient reliability (test-retest reliability and internal consistency) and multiple aspects of validity (e.g., convergent, discriminant, and, predictive validity). For many RDoC constructs and measures, the systematic testing of psychometric properties across units of measure has been a neglected area of study and this was identified by a recent NIMH workgroup on RDoC (149). Psychophysicologists have long argued for the importance of psychometrics and data suggests that ERPs and startle potentiation are psychometrically sound. However, more research and methodological considerations are needed as steps are made towards advancing a more valid classification system.

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