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Methodological issues in the use of individual brain measures to index trait liabilities: The example of noise-probe P3☆

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ABSTRACT

Recent research initiatives have called for an increased use of biological concepts and measures in defining and studying mental health problems, but important measurement-related challenges confront efforts in this direction. This article highlights some of these challenges with reference to an intriguing measure of neural reactivity: the probe P3 response, a mid-latency brain potential evoked by an intense, unexpected acoustic-probe stimulus. Using data for a large adult sample ($N = 418$), we report evidence that amplitude of probe P3 response to unwarned noise bursts occurring in a picture-viewing task exhibits robust, independent associations with two distinct trait constructs: weak inhibitory control (or disinhibition; DIS) and threat sensitivity (THT). Additionally, we report a selective association for THT with attentional suppression of probe P3 response during viewing of aversive pictures compared to neutral. These results point to separable elements of variance underlying the probe P3 response, including one element reflecting DIS-related variations in cognitive-elaborative processing, and others reflecting THT-related variations in aversive foreground engagement and abrupt defensive reorientation. Key measurement issues are considered in relation to these specific findings, and methodological and statistical approaches for addressing these issues are discussed in relation to advancement of a quantitatively sound, biologically informed science of psychopathology.

1. Introduction

Empirical research over the past decade has called into question the categorical classification of psychopathology as reflected in the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013), pointing instead to a dimensional organization of clinical problems cutting across traditional mental disorder categories. In line with this shift, the National Institute of Mental Health (NIMH) has proposed a biologically oriented framework for pursuing research on transdiagnostic problem dimensions, the Research Domain Criteria (RDoC) matrix (Insel et al., 2010). The NIMH RDoC framework calls for investigation of basic biobehavioral processes relevant to differing forms of mental illness using multiple units of analysis, from molecular (genomic) variables to overt behavioral measures. Two RDoC matrix constructs have particular relevance for understanding psychopathology: inhibitory control and threat sensitivity (Blair et al., 2014; Patrick et al., 2012; Patrick & Drislane, 2015; Yancey et al., 2013; Yancey et al., 2016). Weak inhibitory control plays a role in various externalizing conditions, including conduct disorder, adult antisocial behavior, and substance use disorders (Krueger et al., 2002), whereas threat sensitivity has been implicated in fear-related internalizing conditions such as social phobia, specific phobia, and panic disorder (B. D. Nelson et al., 2013). Thus, these two RDoC constructs are relevant to a number of the most commonly occurring mental disorders. A deeper understanding of these constructs in neurobiological terms will thus contribute to new perspectives on a wide range of mental illnesses and help to inform prevention and treatment efforts.

A major topic of interest in biologically oriented clinical research has been the concept of "biomarkers," referring to biological variables that index liabilities for or expressions of psychopathology. In recent years, this concept has come under criticism for its oversimplification of the

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relationship between biological phenomena and outcomes (Lenzenweger, 2013; Miller & Rockstroh, 2013). Across scientific disciplines, the identification of biomarkers for psychopathology has been a major funding priority, but investigative efforts have often failed to consider measurement issues of importance to this endeavor. For example, biomarkers generally account for only a small portion of the variance in clinical outcomes they are intended to index (Patrick & Bernat, 2010; Patrick et al., 2013). Additionally, individual biomarkers can contain variance related to different clinical outcomes, raising questions about their etiological coherence and diagnostic specificity (Cicchetti, 1984). The current study highlights overlooked issues in the use of neurobiological variables to index psychopathology-related characteristics, through reference to a distinct variant of the P3 brain event-related potential (ERP), the noise-probe P3 response.

1.1. Probe P3 as a neural indicator of psychopathology

The noise-probe P3 (or probe P3) is a member of the larger P3 family of brain-ERP responses. (The term "P300" refers to the response to infrequent target stimuli in the well-known oddball task, whereas the more generic label "P3" is used for variants of this response occurring in different tasks [Rugg & Coles, 1995].) Broadly, P3 responses are positive ERP deflections, typically maximal in amplitude at parietal scalp sites, that tend to peak between 300 and 600 ms following the presentation of task stimuli, depending on the context of processing. Prior work using P3 response to visual stimuli suggests that this response reflects cognitive post-processing, with greater amplitude reflecting greater cortical resources devoted to processing of the stimulus's associative meaning or significance (Lang et al., 1992; Rugg & Coles, 1995).

The probe P3 is a variant of this type of ERP response that occurs in response to a sudden, intense acoustic stimulus, such as a burst of white noise. Like other variants of P3, it is a mid-latency response to a salient perceptual stimulus. However, it differs from other P3s in that it is elicited by a stimulus that is inherently noxious, due to its intensity and unpredictability. As such, the probe P3 has been characterized as indexing a "cortical call-to-arms" — a rapid marshalling of cognitive-attentional capacities to interpret and contend with a strong, unanticipated event (Drislane et al., 2013; see also Graham, 1979). Additionally, prior research has demonstrated that, in contrast with the faster-latency (<100 ms) blink-reflex response, which increases during viewing of aversive foregrounds (relative to neutral) and decreases during viewing of pleasurable ones, probe P3 amplitude is reduced for probes presented during both aversive and pleasurable foregrounds (Cuthbert et al., 1998). This effect has been interpreted as reflecting reduced availability of cognitive resources for post-processing of noxious probe stimuli as a function of enhanced foreground-attentional engagement (Cuthbert et al., 1998; Drislane et al., 2013; Graham, 1979).

Thus, while P3 responses are generally viewed as indexing cognitive processing, the probe P3 appears to operate as a biological index of psychological processes related to both cognition and emotion: It indexes a rapid defensive-interrupt process (Graham, 1979; see also Miller et al., 2002) to discern the action-relevance of abrupt, intense events; in addition, it taps into affective-foreground engagement at the time of noise-probe occurrence, as reflected in P3-amplitude suppression during affective relative to neutral foreground contexts. As discussed below, distinct portions of variance in probe P3 reflect 1) cognitive processes in common with other P3 variants and 2) affective processes related to the aversive nature of the probe; these portions of probe-P3 variance are differentially associated with psychopathology-related dispositions.

1.2. Disinhibition (DIS)

One relevant psychological variable in the study of cognitive processing is inhibitory control, represented by the construct of response inhibition in the Cognitive Systems domain of the RDoC matrix. Weak inhibitory control, characterized in individual-difference terms as trait disinhibition (DIS; L. D. Nelson et al., 2016; Patrick et al., 2013), has been identified as a liability factor for externalizing problems of various types, including child and adult antisocial behavior and maladaptive substance use (Krueger et al., 2002; Yancey et al., 2013). Patrick et al. (2013) constructed a "psychoneurometric" index of DIS, incorporating self-report-scale measures along with brain-response variables, that effectively predicted both clinical-symptom and physiological criterion measures. Within this model of disinhibition, amplitude of P3 response to noise probes presented during viewing of neutral pictures was shown to covary with scale measures of DIS as well as with P3 responses to target and novel stimuli in a separate visual oddball task. Results from this study dovetail with other work showing that trait disinhibition is associated with reductions in different variants of P3 response (Bernat et al., 2011; L. D. Nelson et al., 2011; Yancey et al., 2013), indicating that high DIS involves a general, cross-task deficit in cognitive post-processing of task-related stimuli (Patrick et al., 2006; Hall et al., 2007; Venables et al., 2015a). The finding by Patrick et al. (2013) that probe P3 covaried with DIS in a manner similar to target P3 response suggests that the noise-elicited P3 includes an element of variance reflecting this DIS-related impairment in cognitive post-processing. As highlighted above and discussed next, the probe P3 response also appears to contain separate elements of variance related to affective processing that may operate as indices of threat sensitivity.

1.3. Threat sensitivity (THT)

Another psychological characteristic with broad relevance to clinical problems is threat sensitivity (THT), represented by the construct of acute threat in the Negative Valence Systems domain of the RDoC matrix. Conceptualized in individual-difference terms, this construct connects to the general trait dimension shown to underlie psychological-scale measures of fear versus fearlessness in relation to stimuli and situations of various types (Kramer et al., 2012). When operationalized in terms of scores on this fear/fearlessness dimension, variations in threat sensitivity are independent of (i.e., uncorrelated with) variations in inhibitory control, quantified as trait disinhibition (L. D. Nelson et al., 2016; Venables et al., 2015b). High scores on this fear/fearlessness dimension have been found to be related to anxiety disorders of various types, particularly those involving context-bound fear (L. D. Nelson et al., 2016; Yancey et al., 2016); low scores on this dimension, by contrast, are associated with affective-interpersonal ("Factor 1") symptoms of psychopathy (Patrick & Bernat, 2009b; Patrick & Drislane, 2015).

Related to the latter point, a study of incarcerated male offenders by Drislane et al. (2013) reported a negative association between Factor 1 symptoms of psychopathy (as assessed by the Psychopathy Checklist-Revised [PCL-R]; Hare, 2003) and amplitude of probe P3 response during a picture-viewing task (both for noises presented during pictures of differing types and during intervals between pictures). Given prior evidence linking Factor 1 psychopathy features to deficient fear response (e.g., Benning et al., 2005a; Flor et al., 2002; Patrick, 1994), the authors interpreted this result as evidence for a reduced "cortical call-to-arms" in relation to sudden noxious events among offenders exhibiting the core affective-interpersonal symptoms of psychopathy. Based on the notion of a continuum of threat sensitivity ranging from psychopathic fearlessness at one end to fear-disorder susceptibility at the other, individuals high in THT would be expected to show *enhanced* probe P3 amplitude; however, this possibility needs to be tested directly. Notably, and in contrast with above-noted findings from Patrick et al. (2013), Factor 2 features of psychopathy (which relate more to trait disinhibition; Venables & Patrick, 2012) showed only a weak, nonsignificant association with reduced probe P3 response in Drislane et al.'s (2013) study. The null relationship for disinhibitory symptoms of psychopathy in this study may reflect the high prevalence of such symptoms in incarcerated offenders and resultant problems of range