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Variation in reward- and error-related neural measures attributable to age, gender, race, and ethnicity

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ABSTRACT

Event-related potentials (ERPs) have been widely applied to the study of individual differences in reward and error processing, including recent proposals of several ERPs as possible biomarkers of mental illness. A criterion for all biomarkers, however, is that they be generalizable across the relevant populations, something which has yet to be demonstrated for many commonly studied reward- and error-related ERPs. The aim of this study was to examine variation in reward and error-related ERPs across core demographic variables: age, gender, race, and ethnicity. Data was drawn from three studies with relatively large samples (*N* range 207–527). Results demonstrated that ERPs varied across the demographic variables of interest. Several examples include attenuated reward-related ERPs with increasing age, larger error-related ERPs for men than women, and larger ERPs to feedback after losses for individuals who identified as Hispanic/Latino. Overall, these analyses suggest systematic variation in ERPs that is attributable to core demographic variables, which could give rise to seemingly inconsistent results across studies to the extent that these sample characteristics differ. Future psychophysiological studies should include these analyses as standard practice and assess how these differences might exacerbate, mask, or confound relationships of interest.

Event-related potentials (ERPs), with their millisecond temporal resolution, provide a direct measure of brain activity in real time and have significantly contributed to the investigation of a wide range of psychological processes for decades. ERP research has expanded upon basic knowledge of information processing, and clinical applications have elucidated possible biomarkers, or measureable indicators of disease, for a number of psychological disorders (Lenzenweger, 2013). ERPs are an especially useful tool to identify biomarkers for a variety of reasons. First, ERP studies are more cost-efficient than other neuroimaging techniques, greatly increasing the feasibility of conducting large, multi-site studies (cf. Hesselbrock et al., 2001; Tenke et al., 2017). EEG recording procedures also are well tolerated by participants of all ages and can be modified for a wide range of muscular and intellectual abilities. The temporal measurement precision and reduced financial burden and ease of administration also provide ERPs with the capacity to feasibly track change over time with regard to illness onset, illness progression, and treatment efficacy (Luck et al., 2011). Indeed, previous work has demonstrated the capacity of ERPs to prospectively predict illness onset, above and beyond other known risk factors (Bress et al., 2013a; Nelson et al., 2016), and therapeutic response (Schall et al., 1999). Together, the body of research certainly suggests that ERPs are promising tools to yield biomarker candidates for various psychopathologies including schizophrenia, anxiety, and depression (Luck et al., 2011; Olvet and Hajcak, 2008; Proudfit, 2015). However, there are several considerations, one of which will be addressed in the current study, before such claims can be made (Lenzenweger, 2013).

First, biomarker relationships should be specific to a given illness. Second, to enhance functional utility, biomarkers must be reliable. Third, and of particular note for this study, biomarkers must be assessed for applicability, equivalence, and nuance across the populations for which they will be used. The National Institutes of Health (NIH) has made significant strides to ensure this latter consideration. In 2001, The Public Health Service Act mandated that all NIH-funded research include women and minority groups in clinical research, barring scientific exemptions. More recently in 2015, NIH made this mandate stricter in the Consideration of Sex as a Biological Variable in NIH-funded Research (Notice Number NOT-OD-15-102), which requires funded research to consider biological sex influences in analyses, rather than merely recruiting these subjects and not assessing these differences (National Institutes of Health, 2015). In turn, ERP researchers conducting clinical studies must change their current general procedures to report effects of demographic variables on outcomes of interest, regardless of the specific aim of the study. An additional challenge is that ERP studies are commonly underpowered to detect such

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effects—especially with regard to race and ethnicity, due to small samples of these groups, and age, due to the restricted range that is inherent in student samples.

While these three biomarker arguments apply to all ERPs, and certainly all biological measures more generally, we focus here on a subset of well-studied ERPs relevant to reward and error processing, each of which has established links with clinical populations: the P300 (also referred to as the P3), the reward positivity (RewP; also referred to as the *FRN* or *FN*, for a review see Proudfit, 2015), and the error-related negativity (ERN). The P3, a positive deflection in the waveform approximately 300–500 ms after stimulus presentation, reflects attentional allocation to unexpected, infrequent, or otherwise salient stimuli (Donchin and Coles, 1988; Hillyard and Kutas, 1983; Polich, 2007; Novak and Foti, 2015). Relevant to reward processing, the P3 is elicited by cues signaling potential rewards (i.e., Cue-P3), as well as feedback indicating reward outcomes (i.e., fb-P3). The RewP, a positive deflection in the waveform approximately 300 ms after feedback indicating a reward, reflects the early, initial evaluation of outcomes as better or worse than expected (Bismark et al., 2013). The ERN, a negative deflection in the waveform within the first 100 ms after commission of an error on speeded tasks, captures early, preconscious error detection and is sensitive to factors such as error saliency and uncertainty (Falkenstein et al., 1990; Holroyd and Coles, 2002; Jackson et al., 2015). Below, we discuss each of these ERPs and their potential as illness biomarkers in greater detail.

Research concerning the utility of the P3 as a biomarker for schizophrenia is building. A meta-analysis assessing differences in P3 amplitude across individuals with and without schizophrenia diagnoses demonstrated that the P3 seemed to be blunted, although present, in those with schizophrenia compared to controls (Bramon et al., 2004; Jeon and Polich, 2003) and seems to serve as a trait-like marker with high test-retest reliability among patients (Mathalon et al., 2000; Turetsky et al., 1998a). Moreover, P3 amplitude may be able to identify individuals at risk prior to onset (Bramon et al., 2008; Frommann et al., 2008; Özgürdal et al., 2008), with an ability to predict transition to psychosis even within a high-risk sample (Nieman et al., 2014; van Tricht et al., 2010). In addition to group differences and earlier markers, the P3 also has been used successfully to predict which patients with schizophrenia will benefit from specific treatments (Schall et al., 1999).

The RewP, an ERP response to reward delivery, has been demonstrated to share relationships with several individual differences including behavioral and self-reported sensitivity to reward (Bress et al., 2012). Subsequently, reduced RewP amplitudes are related to increased depression symptomatology in both adults (Foti and Hajcak, 2009; Foti et al., 2014) and children (Bress et al., 2012). For the RewP, blunted activity seems to be related specifically to depressive, and not anxious, symptoms (Bress et al., 2013b). Perhaps most promising, the RewP also has demonstrated stability akin to a neurophysiological trait and seems to predict the future onset of depression, above and beyond other known risk factors such as maternal depressive history and current depressive symptoms (Bress et al., 2013a; Kujawa et al., 2014; Nelson et al., 2016). The RewP does not seem to be a fixed genetic biomarker of disorder, however, as one interesting line of research suggests that supportive parenting may alter this neurophysiological risk factor (Kujawa et al., 2015).

Similar to the P3 and RewP, the ERN also has been discussed as a potential biomarker. Specifically, the ERN may serve as an endophenotype, a specific type of biomarker that is an intermediary between genotypes and phenotypes (Gottesman and Gould, 2003), for anxiety-related disorders including obsessive-compulsive disorder (OCD) and generalized anxiety disorder (GAD; Olvet and Hajcak, 2008). Research supporting this proposal has demonstrated that the ERN is enhanced in individuals with OCD and GAD (Gehring et al., 2000; Johannes et al., 2001; Ruchsow et al., 2005; Ladouceur et al., 2006). Consistent with the definition of an endophenotype, the ERN in this population does not seem to fluctuate with state-related changes, such as after symptom reduction via treatment (Hajcak et al., 2008) or increased situational anxiety (Moser et al., 2005), and thus may be considered trait-like. Moreover, preliminary work also has shown strong heritability estimates for the ERN, suggesting this ERP may also track predispositions for psychopathology across generations (Anokhin et al., 2008), although parenting style also seems to be a significant contributor to ERN amplitudes (Meyer et al., 2015).

Pertaining to the scientific considerations to be assessed for biomarkers, each of the ERP components discussed here has been found to have strong to excellent reliability across trials in a single session and sessions across time (Fabiani et al., 1987; Segalowitz and Barnes, 1993; Olvet and Hajcak, 2009; Huffmeijer et al., 2014; Bress et al., 2015). Ascertaining specificity between ERP and illness has been more problematic to date. For example, although the P3 has noteworthy relationships with schizophrenia, it also shares relationships with a variety of other impairments such as Alzheimer's disease (for a review see Turetsky et al., 2015). Some research seeking to clarify ERP/psychopathology relationships has been conducted (Horan et al., 2012; Olvet and Hajcak, 2008). However, these relationships need to be further refined with continued research. ERPs may not be related only to diagnoses but rather may better be utilized to parse heterogeneity within diagnostic groups—according to specific symptom profiles, cognitive deficits, or affective, and interpersonal styles (Luck et al., 2011).

Lastly, perhaps the greatest remaining candidate biomarker consideration is the need for potential ERPs to be assessed for applicability, equivalence, and nuance across the populations for which they will be used. Previous research has suggested that the P3 is influenced by both age and gender, as it seems to be reduced for older adults (Knight, 1987; Patterson et al., 1988) and smaller in men than women (Turetsky et al., 1998b). The ERN also seems to vary across the lifespan—first emerging as early as age 7 (Hajcak et al., 2008; Kim et al., 2007; Wiersema et al., 2007), increasing until it peaks in late adolescence or early adulthood (Davies et al., 2004a; Davies et al., 2004b), and perhaps decreasing in size for older adults (Band and Kok, 2000; Mathewson et al., 2005; Nieuwenhuis et al., 2002). One line of research also has suggested that the ERN's relationship to anxiety may be found specifically in women and not in men (Moran et al., 2012; Moser et al., 2016). The RewP seems to vary systematically across gender such that men generally have larger responses (Crowley et al., 2009; Crowley et al., 2013); however this varies depending on experimental factors, such as size of the reward (Grose-Fifer et al., 2014). However, despite the mandate that demographically diverse samples be included in clinical experiments, and the possible (plausible) differences across these variables, related inquiries are infrequently examined or even merely reported in ERP research (Keil et al., 2014).

The aim of the current study is to investigate main effects of demographic differences on the aforementioned ERPs. We were primarily interested in the P3, RewP, and ERN given their large clinical literatures. In addition, one reward task we utilized was the monetary incentive delay (MID) task, which also gives other potentially relevant ERP indicators: the contingent negative variation (CNV) and stimulus-preceding negativity (SPN; Novak et al., 2016). The CNV and SPN are both negative deflecting slow waves, associated with cued motor preparation and anticipation of feedback, respectively (Brunia et al., 2012; Foti and Hajcak, 2012; Kotani et al., 2003; Ohgami et al., 2004; Ohgami et al., 2006). More specifically, and within the MID framework, the CNV is associated with preparation for motoric activity for an anticipated target, whereas the SPN tracks anticipation of performance-based feedback. The error monitoring task we utilized also gives another potentially relevant ERP indicator, the error positivity (Pe). The Pe is a positive slow wave, associated with the conscious awareness of having made an error (Falkenstein et al., 2000; Hohnsbein et al., 1989; Nieuwenhuis et al., 2001). The present sample was extracted from several existing datasets (e.g., Ait Oumeziane and Foti, 2016; Hill et al.,