Journal of Anxiety Disorders 54 (2018) 1–10

Contents lists available at ScienceDirect

Journal of Anxiety Disorders

journal homepage: www.elsevier.com/locate/janxdis

The effect of panic disorder versus anxiety sensitivity on event-related potentials during anticipation of threat

Elizabeth S. Stevens[a], Anna Weinberg[b], Brady D. Nelson[c], Emily E.E. Meissel[a], Stewart A. Shankman[a,*]

[a] Department of Psychology, University of Illinois at Chicago, IL, USA
[b] Department of Psychology, McGill University, Quebec, Canada
[c] Department of Psychology, Stony Brook University, NY, USA

ARTICLE INFO

Keywords:
Anxiety sensitivity
Panic disorder
Event-related potentials
Predictability
Attention

ABSTRACT

Attention-related abnormalities are key components of the abnormal defensive responding observed in panic disorder (PD). Although behavioral studies have found aberrant attentional biases towards threat in PD, psychophysiological studies have been mixed. Predictability of threat, an important feature of threat processing, may have contributed to these mixed findings. Additionally, *anxiety sensitivity*, a dimensional trait associated with PD, may yield stronger associations with cognitive processes than categorical diagnoses of PD. In this study, 171 participants with PD and/or depression and healthy controls completed a task that differentiated anticipation of predictable vs. unpredictable shocks, while startle eyeblink and event-related potentials (ERPs [N100, P300]) were recorded. In all participants, relative to the control condition, probe N100 was enhanced to both predictable and unpredictable threat, whereas P300 suppression was unique to predictable threat. Probe N100, but not P300, was associated with startle eyeblink during both threatening conditions, and was strongest for unpredictable threat. PD was not associated with ERPs, but anxiety sensitivity (physical concerns) was positively associated with probe N100 (indicating reduced responding) in the unpredictable condition independent of PD diagnosis. Vulnerability to panic-related psychopathology may be characterized by aberrant early processing of threat, which may be especially evident during anticipation of unpredictable threats.

1. Introduction

Heightened defensive motivation is a key feature of many internalizing psychopathologies (i.e., anxiety disorders and depression; Lang, 1995; McTeague & Lang 2012). In panic disorder (PD), heightened defensive responding manifests as intense fear (i.e., panic attacks) and anxious apprehension of potential future panic attacks (Barlow, 2000). Learning-based conceptualizations of PD postulate that a key mechanism in PD is the *unpredictability* of panic attacks (Bouton, Mineka, & Barlow, 2001), which in turn leads to anticipatory anxiety about having subsequent panic attacks.

The importance of unpredictability is further highlighted by a growing literature demonstrating that *predictable* threats yield qualitatively different responses from *unpredictable* threats, with the former yielding fight-flight-freeze responses and the latter yielding more sustained states of preparedness for potential threat (Grillon, 2002; Shankman et al., 2013). The distinction between predictable and unpredictable threat has been validated by non-human animal (Davis, 1998, 2006; Gray & McNaughton, 2000), pharmacological challenge (Grillon et al., 2006; Grillon et al., 2009; Moberg & Curtin, 2009), and neuroimaging (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011) studies. To examine differences in defensive responding to predictable versus unpredictable threat, Grillon and colleagues developed the No-Predictable-Unpredictable (NPU) threat task (Schmitz & Grillon, 2012). There are three conditions in the NPU task: (1) no threat, (2) predictable threat (i.e., threat is signaled by a cue), and (3) unpredictable threat (i.e., threat is unsignaled and may be presented at any time). Defensive responding is typically operationalized as the magnitude of the startle eyeblink reflex to loud acoustic startle probes, and has been shown to be enhanced during predictable and unpredictable threat conditions relative to the no threat condition (Gorka, Lieberman, Shankman, & Phan, 2017; Grillon et al., 2009; Nelson et al., 2013;

Abbreviations: PD, panic disorder; ERP, event-related potential; MDD, major depressive disorder; NPU, No-Predictable-Unpredictable; AS, anxiety sensitivity; PC, physical concerns; CC, cognitive concerns; SC, social concerns; PCA, principal components analysis; EMG, electromyography; EEG, electroencephalography; ANOVA, analysis of variance; ANCOVA, analysis of covariance

* Corresponding author.
E-mail address: stewarts@uic.edu (S.A. Shankman).

https://doi.org/10.1016/j.janxdis.2017.12.001
Received 22 May 2017; Received in revised form 14 November 2017; Accepted 12 December 2017
Available online 15 December 2017
0887-6185/

Shankman et al., 2013).

A few studies have examined the association between PD and the startle reflex during the NPU-threat task. Grillon et al. (2008) found that patients with PD, relative to healthy controls, exhibited greater startle potentiation to unpredictable threat, but did not differ on response to predictable threat. Shankman et al. (2013) sought to extend these findings by administering the NPU-threat task to individuals with PD without major depressive disorder (MDD), PD with MDD, and MDD without PD. Individuals with PD (irrespective of comorbid MDD), but not those with MDD only, exhibited heightened startle potentiation to unpredictable threat but unlike Grillon et al. also exhibited heightened startle potentiation to predictable threat. Furthermore, startle potentiation to *unpredictable* threat was uniquely associated with family history of PD, independent of participant diagnosis of PD (Nelson et al., 2013). These results suggest that response to threat, and perhaps only unpredictable threats, is a key feature of PD.

Another important component of defensive responding is attentional engagement with threat (Lang, 1995). Studies examining attentional biases to threat among individuals with PD have yielded mixed results, with some studies finding greater attentional bias toward threat- and/or panic-related stimuli (Lundh, Wikström, Westerlund, & Öst, 1999; Reinecke, Cooper, Favaron, Massey-Chase, & Harmer, 2011) and others finding no differences from controls (De Cort, Hermans, Spruyt, Griez, & Schruers, 2008; Kampman, Keijsers, Verbraak, Naring, & Hoogduin, 2002).

One explanation for these discrepant findings is that the behavioral measures typically used to assess attentional biases, such as the dot probe paradigm (MacLeod, Mathews, & Tata, 1986), have poor reliability (Kappenman, Farrens, Luck, & Proudfit, 2014; Schmukle, 2005), potentially due to the temporal and neurophysiological separation between the construct being measured (i.e., attention) and the behavior indexing the construct (e.g., motoric response selection). In contrast, ERP indices of attention have better psychometric properties, (Levinson, Speed, Infantolino, & Hajcak, 2017; Segalowitz & Barnes, 1993), in part because of their closer temporal proximity to attentional processes. Although the startle eyeblink reflex is sensitive to individual differences in attention (Blumenthal et al., 2005), another advantage of ERP measures of attention-related processes is that they can distinguish different *components* of attention. Given evidence that anxiety specifically influences early, automatic attentional processes, as opposed to later, more elaborative stages of attentional processing (Weinberg & Hajcak, 2011; Weinberg, Perlman, Kotov, & Hajcak, 2016), it is particularly important to isolate early attentional components.

ERPs that index attention-related processes can be measured during the NPU-threat task by examining ERPs to startle probes during each condition. Probe-elicited ERPs differentiate several components of cognitive processing that likely relate to attention − most notably an N100 and a P300 (Cuthbert, Schupp, Bradley, McManis, & Lang, 1998; Schupp, Cuthbert, Bradley, Birmaumer, & Lang, 1997). The N100 is a negative-going deflection that likely indexes early attention and sensory processing (Cuthbert et al., 1998). The P300 is a positive-going deflection that likely reflects, in part, allocation of attention to salient stimuli, regardless of valence (Cuthbert et al., 1998). In prior threat-of-shock and affect modulation studies, the probe N100 is enhanced in threat or aversive relative to “safe” or positive conditions (Al-Abduljawad, Baqui, Langley, Bradshaw, & Szabadi, 2008; Cuthbert et al., 1998). In contrast, the probe P300 is attenuated; rather than attending to salient startle probes, attention is allocated to the more salient threatening context (Cuthbert et al., 1998; Shackman et al., 2011).

Our group previously investigated ERPs to startle probes during the NPU-threat paradigm in a sample of undergraduates (Nelson, Hajcak, & Shankman, 2015). Probe N100 was enhanced during the *unpredictable* (versus no threat) condition, but not during the predictable threat condition, suggesting that unpredictable threatening contexts may particularly increase this early sensory/attentional component. In contrast, probe P300 was attenuated during both predictable and unpredictable conditions relative to the no threat condition, suggesting that participants’ attention to salient contexts (i.e., threat of shock) may have increased to both threat conditions.

While several studies have examined the association between PD and the probe N100 and P300 (albeit with equivocal results; Clark, McFarlane, Weber, & Battersby, 1996; Di Giorgio, Velasques, Ribeiro, Nardi, & de Carvalho, 2015), no study has examined whether threat predictability impacts the association between PD and these ERP components. Given our aforementioned finding that familial vulnerability for PD was only related to startle eyeblink potentiation to unpredictable threat (Nelson et al., 2013), aberrant processing of threat in PD indexed by these ERPs may also be specific to unpredictable threats. The primary aim of the present study was therefore to extend the EMG startle findings of Shankman et al. (2013) by examining the association between ERP indices of attention-related processes and PD during predictable and unpredictable threatening contexts.

Studies of attentional deficits in PD may have yielded mixed results also because PD was defined categorically. Numerous studies of multiple psychopathologies have shown that a categorical conceptualization of psychopathology might not ‘carve nature at its joints’ and that a dimensional conceptualization likely has greater validity than categorical diagnoses (Helzer, Kraemer, & Krueger, 2006; Kendell & Jablensky, 2003). Given that PD and its mechanisms are heterogeneous, studies that define participants by individual differences on particular sensitivities rather than by categorical DSM diagnoses might have better predictive validity. Anxiety sensitivity (AS) is one such dimension that is principally relevant to PD (Taylor & Fedoroff, 1999). AS is a clinical trait that reflects sensitivity to physical sensations associated with threat responding that are perceived as harmful or having cognitive or social consequences, and has been shown to connote vulnerability for multiple psychopathologies (Epkins, Gardner, & Scanlon, 2013; Schmidt, Lerew, & Jackson, 1997; Taylor & Fedoroff, 1999).

Moreover, AS has been shown to be associated with attentional vigilance for physical threat-related words (e.g., breathless, harm; Keogh, Dillon, Georgiou, & Hunt, 2001; Teachman, Smith-Janik, & Saporito, 2007; but see Lang & Sarmiento, 2004 for null results). Consistent with these findings, Nelson, Hodges, Hajcak, & Shankman, (2015) reported that high levels of AS were associated with greater probe N100 enhancement during anticipation of unpredictable threat and greater probe P300 suppression in anticipation of both predictable and unpredictable threat. These findings suggest that AS is associated with altered patterns of attentional/cognitive processing of threat. Despite promising results, Nelson, Hodges et al. (2015) examined this question in a sample of college students (which tend to be healthier than clinical samples; Coyne, 1994) resulting in a restricted range of AS scores, preventing generalization to clinical populations. Thus, the second aim of the present study was to examine, in a clinical sample, the association between a continuous measure of anxiety (i.e., AS) and the probe N100 and P300 during the NPU-threat task.

Given the high rates of comorbidity between anxiety and MDD (Shankman & Klein, 2003), it is important to isolate the effects of these conditions on cognitive processing (Miller & Chapman, 1985). Extant research indicates a strong relationship between anxiety and unpredictable threat responding, whereas findings regarding MDD are mixed (Grillon et al., 2013; Shankman et al., 2013). Additionally, because anxiety is characterized by deficits in early cognitive processes, whereas MDD is characterized by disruptions in later, elaborative processing (Sass et al., 2014; Weinberg et al., 2016), alterations in relatively early ERP components such as the N100 and P300 are likely to be unique to individuals with anxiety.

In sum, the present study seeks to extend the EMG startle findings