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Event-related potential and autonomic signs of maladaptive information processing during an auditory oddball task in panic disorder

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ABSTRACT

Various empirical data suggest that individuals with Panic Disorder (PD) fail to appropriately assign significance to sensory stimuli within the internal and external milieu, including those stimuli which are patently threat-neutral. The failure to appropriately discriminate 'signal' stimuli from among 'noise' signals [Gordon, E., Liddell, B.J., Brown, K.J., Bryant, R., Clark, C.R., Das, P., et al. 2007. Integrating objective gene–brain-behavior markers of psychiatric disorders. J. Integr. Neurosci. 6, 1–34.] results in disturbances of information processing and attentional deployment, which manifests across multiple levels of functioning (e.g., brain, behaviour, autonomic). The present event-related potential (ERP) study, therefore, investigated attentive information processing in PD, using a standard two-tone auditory oddball paradigm, to assess patients' response to infrequent 'target' tones (i.e., signals) and frequent 'non-target' tones (i.e., noise). Simultaneously-recorded autonomic data provided converging measures of the concomitants of disordered information processing. PD patients ($n=50$) showed increased N1 amplitude to frequent non-target tones and reduced P3 amplitude to infrequent targets, compared to matched controls ($n=98$). There were no between-group differences for N1 targets, N2 or P2. Patients additionally showed increased heart rate, fewer spontaneous skin conductance responses (trend) to significant stimuli, and reduced P3 latency compared to controls, although the latter result was accounted for by patients who frequently experienced depersonalization and/or derealisation during panic. Patients showed several disturbances of attentive information processing in a simple auditory discrimination task: Increased N1 to repeated stimuli suggests impaired stimulus filtering, whereas reduced P3 amplitude and latency represent the under-allocation of neural resources for infrequent, goal-relevant stimuli, and their increased speed of processing, respectively. These disturbances likely contribute to patients' aversive outcomes in stimulus-rich environments.

1. Introduction

Converging empirical data from clinical observations and behaviour-based and psychophysiological studies suggest that individuals with Panic Disorder (PD) with or without agoraphobia characteristically engage in the maladaptive deployment of attention, secondary to disturbances of sensory information processing. Various behavioural data indicate that panic disordered individuals maintain an excessively self-focused attention and are preoccupied with disorder-related thoughts and imagery, while showing a concomitant reduction of attention to their external environment (Hayward et al., 2000; Kallai, 1995; Ottaviani and Beck, 1987; Schmidt et al., 1997; Watts, 1989; Wells and Papageorgiou, 1999). Furthermore, these data show that maladaptive, self-directed attentional focus in PD may, given the capacity-limited nature of human information processing systems, impair the processing of even salient environmental information. For example, Hayward et al. (2000) found that PD patients, because of their inability to override their tendency for self-focused attention, were incapable of complying with experimental instructions to externally focus their attention. Data from information processing paradigms show that these overt manifestations of maladaptive attentional deployment in PD are associated with both pre-attentive and attentive disturbances of threat-contingency evaluation for somatic stimuli (Khawaja and Oei, 1998; McNally, 1998; Mobini and Grant, 2007; Pauli et al., 2005).

However, a characterization of attentional focus and information processing in panic disorder according to a single internal/external continuum is an over-simplification, as various empirical data indicate the over-inclusion of certain environmental stimuli in PD. For example, individuals with PD are highly distractible and demonstrate a failure, both pre-attentively and attentively, to inhibit a variety of irrelevant (Kampmann et al., 2002; Ludewig et al., 2002, 2005; van den Hueval et al., 2005; Windmann et al., 2002), and specifically

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repetitive (Ghisolfi et al., 2006; Hazell and Wilkins, 1990) non-somatic stimuli. Additionally, event-related potential (ERP) data suggest that novel acoustic stimuli, irrespective of their relevance, may more readily capture the attention of panic disordered, as compared to healthy, individuals (Clark et al., 1996). Indirect evidence of the over-inclusion of certain types of environmental stimuli is the clinical observation that panic disordered individuals frequently experience heightened anxiety and panic in complex environments of particularly high sensory load: common agoraphobic and panic-triggering situations such as supermarkets, shopping malls and crowds (Street et al., 1989; Sadock and Sadock, 2005) may be characterized as such.

Taken together, these varied data suggest that individuals with PD show a reduced ability to appropriately assign significance to stimuli within both the internal and external milieu, resulting in the inappropriate allocation of attentive (and pre-attentive) processing resources. Such disordered information processing, characterized by a breakdown in adaptive 'signal' to 'noise' discrimination functions (i.e., the ability to focus on relevant information and to suppress irrelevant information), is proposed to be central to the clinical phenomenology of major psychiatric disorders, including anxiety disorders (c.f. Compton, 2003; Gordon et al., 2007). Disorder-specific signals such as innocuous bodily sensations (Beck and Clark, 1997; Windmann, 1998) and those signifying escape-impedance (Jones et al., 1996), and also innate threat signals including novelty (c.f. Gordon et al., 2007), inappropriately elicit threat meaning assignments, and are preferentially processed: other (threat-neutral) stimuli, vying for access to capacity-limited higher cortical processing, would therefore be poorly discriminated.

ERP investigations of the processing of relevant ('signal') and irrelevant ('noise') threat-neutral stimuli in PD have typically used variants of an auditory oddball paradigm to yield temporally-precise indices of continuous sensory information processing spanning the N1 (early-attentive) to P3 [1] (attentive) latency range. To date, however, this literature has yielded inconsistent, and at times contrary, findings. Increased N1 amplitude to irrelevant oddball stimuli (frequent non-targets: Iwanami et al., 1997; Ogura, 1995), and to repeated auditory stimuli in a passive listening task (Knott et al., 1991) have been reported. As N1 reduces upon repeated presentation of an auditory stimulus (Budd et al., 1998; Sambeth et al., 2004) in order to filter out repetitive behaviourally-irrelevant stimuli (Boutros et al., 1999) increased N1 amplitude to repetitive stimuli suggests a reduced ability to discard stimuli of low significance in PD. Iwanami et al. (1997) additionally found increased N1 to relevant oddball stimuli (infrequent targets), which correlated with self-reported state anxiety in PD, suggesting a contribution of cortical arousal. In contrast, other investigators reported no group effect for N1 (e.g., Clark et al., 1996; Wang et al., 2003). Increased P3a to rare target and distractor tones within a three-tone oddball task (Clark et al., 1996) and decreased P3 amplitudes to target tones within a standard two-tone oddball task (Gordeev, 2008) have been reported, reflecting disturbances in passive and active attentional mechanisms in PD, respectively (Muller-Gass and Campbell, 2002). Furthermore, both reduced (Hanatani et al., 2005) and prolonged (Ogura, 1995; Turan et al., 2002) P3 latencies in PD have been reported, suggesting abnormal speed of information processing.

Likely causes of this literature's discordant results include both within- and between-sample clinical heterogeneity, typical use of small study samples, and paradigm differences (e.g. two vs. three tones, button-presses vs. counting targets). Additionally, patients' use of medication including benzodiazepines, and the substantial co-morbidity typical for PD (Kessler et al., 2006; Kroenke et al., 2007) may have confounded some results. A further factor complicating between-study comparison is that some studies, focusing on specific stages of information processing, have reported results only for components of interest.

In parallel with the ERP literature, a largely separate body of research has examined autonomic functioning in PD. In contrast to current conceptualizations of healthy physiology that emphasize the importance of adaptive physiologic responsiveness to ever-changing environments (e.g. Friedman, 2007), panic disordered patients both in and out of the laboratory demonstrated 'diminished physiological flexibility', that is, a diminished range of adaptive autonomic response to non-pathology-specific minor stressors and events, and delayed physiologic habituation (Hoehn-Saric et al., 1991, 2004, 2007; McRaty et al., 2001). Pathology-specific stressors (Hoehn-Saric, 2007) and innately threatening stressors such as novel environments (Larsen et al., 1998), in contrast, elicit exaggerated autonomic responses. These peripheral psychophysiological data provide converging evidence of impaired signal discrimination in PD.

The present study used a standard two-tone auditory oddball task to comprehensively investigate the various stages of attentive sensory information processing in PD. One of the major differences in this study, in contrast to previous such studies, is that concomitantly-recorded autonomic and central measures were obtained. Mean heart rate (HR) and the number of specific skin conductance responses (SCRs) during task performance served as our indices of tonic and phasic peripheral functioning, respectively. Specific SCRs index phasic changes in autonomic activity that signal the orienting of attention towards significant events (Williams et al., 2000). As Panic Disorder comprises a complex of neurophysiologic, autonomic, cognitive and behavioural responses, integrative assessment spanning multiple dimensions may better reveal the matrix of pathophysiologic mechanisms underpinning PD than uni-dimensional analyses. By using a large clinical sample, subgroup analyses will be adequately powered to allow an examination of confounds such as medication use and co-morbidity, which may explain some of the contradictory findings in the literature. Additionally, as PD with symptoms depersonalization and/or derealisation [2] may represent a more severe form of the disorder (Ball et al., 1997; Bovasso and Eaton, 1999; Cassano et al., 1989; Marquez et al., 2001; Segui et al., 2000) that is biologically distinguishable from PD in their absence (Gulsun et al., 2007; Locatelli et al., 1993), and both transient and chronic depersonalization are associated with cortical abnormalities (Phillips and Sierra, 2003; Sierra and Berrios, 1998) the relationship between these symptoms and ERP measures will be examined.

Given the inconsistencies, conflicting findings, and potential confounds within the ERP literature, we have additionally drawn on a broader empirical literature (see above), in order to generate specific ERP hypotheses. Accordingly, we expected patients, relative to controls, to show increased N1 amplitude to non-target tones (reduced filtering of repetitive stimuli), and reduced P3 amplitude to target tones (reduced active control of attentional focus). Additionally, we predicted increased HR (increased autonomic tonus in response to the novel testing environment) and fewer SCRs (reduced phasic orienting to threat-neutral yet salient environmental stimuli) in PD. The extant literature did not permit specific predictions concerning the relationship between central and peripheral measures, nor regarding the ERP correlates of depersonalization.

[1] As P3 is considered a multi-component phenomenon (Polich, 2007) the generic term P3 will be used herein to denote the P3b component, to distinguish it from the earlier frontocentrally maximal P3a.

[2] The generic term depersonalization will be used in this manuscript to denote the symptoms of both depersonalization and derealisation. As per DSM-IV panic attack criteria, the Panic Attack Diary, our measure of the frequency of these symptoms did not distinguish between the two.