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Mismatch negativity indices of enhanced preattentive automatic processing in panic disorder as measured by a multi-feature paradigm

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ABSTRACT

Panic disorder (PD) is a mental disorder characterized by recurrent panic attacks and worrying about having subsequent attacks. Mismatch negativity (MMN) has been established as a correlate of preattentive automatic processing. The aim of the present study is to investigate the preattentive automatic information processing in PD patients as measured by MMN. Subjects included 15 medication-free patients with a DSM-IV diagnosis of PD and 15 age-matched healthy volunteers. MMN was investigated using event-related potentials. The protocol used a multi-feature paradigm. Mean amplitudes and peak latencies were subjected to repeated-measures ANOVAs. PD patients showed a significantly increased MMN of sound intensity and location compared with healthy participants. The correlation between the amplitudes of intensity-MMN and disease severity was also significant. These data provide evidence of anomalous preattentive automatic information processing in PD patients. In particular, the abnormality may be specific for PD.

1. Introduction

Panic disorder (PD), also known as acute anxiety, is characterized by recurrent panic attacks and a change in behavior, such as phobic avoidance and worrying about subsequent attacks (Bouton, Mineka, & Barlow, 2001; Katon, 2006; Roy-Byrne, Craske, & Stein, 2006). The core feature of PD is a panic attack that is seemingly sudden and unexpected. Most patients with PD often have an intense feeling of fear and apprehension with regard to impending death, accompanied by several physical symptoms that usually reach a peak quickly. Patients have an excessive need for medical services with development of PD, leading to impaired social and work life, and an overall reduced quality of life (Olatunji, Feldner, Karekla, & Forsyth, 2008).

Some indirect findings have hinted that anomalies in preattentive or early automatic processing may be the main pathogenesis of PD. For example, Ghisolfi et al. (2006) reported that patients with PD show deficit P50 suppression, which represents diminished sensory gating. Studies on the startle reflex in patients with PD also indicate generalized difficulty suppressing or gating information (Ludewig et al., 2005; Ludewig, Ludewig, Geyer, Hell, & Vollenweider, 2002). Other event-related potential (ERP) studies that used a standard two-tone oddball task indicate that the N1 amplitude of frequent non-target tones is significantly larger in patients with PD (Wise, McFarlane, Clark, & Battersby, 2009). Iwanami, Isono, Okajima, and Kamijima (1997) found significantly increased N1 and N2 amplitudes for target tones and N1 amplitudes for non-target tones in patients with PD. In contrast, some studies have failed to show a significant group effect for an N1 abnormality (Clark, McFarlane, Weber, & Battersby, 1996; Wang et al., 2003). Furthermore, Wang et al. (2003) demonstrated reduced P2 amplitude for the non-target waveforms and attenuated N200 amplitude with a topographical difference over the parietal area for the target waveforms in patients with PD. Hanatani et al. (2005) observed that the latencies of P2, N2, and P3 are shorter, and that patients with PD have shortened N1–P2 interpeak latencies compared with those with generalized anxiety disorder (GAD) and control groups. Taken together, the abovementioned evidence suggests alterations in early information processing in patients with PD.

Mismatch negativity (MMN) is an endogenous ERP component elicited by any discriminating change in the auditory stimulus stream. As MMN is elicited in the absence of attention, it is frequently assumed to reflect pre-attentive memory-based automatic processing (Näätänen, Gaillard, & Mantysalo, 1978; Näätänen,

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Paavilainen, Rinne, & Alho, 2007; Näätänen & Winkler, 1999). The generation of MMN has been attributed to the automatic comparison between the frequent standard stimulus and the infrequent deviant stimulus. MMN-related psychopharmacology is not fully understood yet. However, initial evidence shows that glutamate and gamma-aminobutyric acid are involved in generating MMN, and that serotonin and acetylcholine may modulate MMN indirectly (Kenemans & Kahkonen, 2010). As MMN can be measured even in animals such as rats, it may provide a useful biomarker for assessing the effects of drugs developed to treat the cognitive and functional impairments of patients with PD.

The traditional oddball paradigm, which consists of one or two types of deviants, has been the most widely used paradigm in past decades. However, a relatively longer measurement time is required if more than two types of deviants are investigated. Thus, such a time-consuming measurement is inappropriate because of the limited endurance of clinical patients. Näätänen, Pakarinen, Rinne, and Takegata (2004) developed a multi-feature paradigm in which five different acoustic deviants are presented in the same block within a short period of time. Every second sound varies in frequency, intensity, duration, and sound-source localization, or has a gap in the middle of the tone compared with the standards. Thus, deviants are measured in 50% of all stimuli, with only 10% of deviants in each parameter. This time-efficient procedure may be of particular interest to clinical research when several types of stimuli must be investigated. In fact, it has been applied to research involving several diseases and healthy humans (Fisher, Labelle, & Knott, 2008; Kujala et al., 2007, 2010; Kujala, Lovio, Lepisto, Laasonen, & Näätänen, 2006; Lovio et al., 2009; Menning, Renz, Seifert, & Maercker, 2008; Thonnessen et al., 2008).

Until now, MMN has been investigated in many diseases, such as dyslexia (Kujala, Belitz, Tervaniemi, & Näätänen, 2003; Sebastian & Yasin, 2008), schizophrenia (Bramon, 2004; Fisher et al., 2008; Light & Braff, 2005), Alzheimer's disease (Pekkonen, Hirvonen, Jaaskelainen, Kaakkola, & Huttunen, 2001), depression (Chang et al., 2011; Lepisto et al., 2004), and post-traumatic stress disorder (Menning et al., 2008). However, little is known about MMN in patients with PD, except from one study in our group (Li, Xu, Zhao, Liu, & Zhang, 2007). The study showed that the frequency MMN amplitude in patients with PD increased significantly in the 60–210 ms time window compared with that in normal controls. However, the medication effect (e.g., antidepressants or benzodiazepines) was not eliminated in this study, which made the results less reliable. As the MMN was formerly categorized as an early N2a subcomponent (Folstein & Van Petten, 2008), it would be useful to mention the work on N2a in patients with PD. In a study focusing on N200, the reduction in N2a peak amplitude in patients with PD approached significance. However, it was obvious that the effect of selective attention could not be excluded from an active discrimination task protocol. Thus, N2a in this condition was difficult to index as MMN.

The aim of the current study was to investigate preattentive automatic information processing in medication-naive patients with PD. In particular, a multi-feature paradigm was used in this study. The dysfunction of preattentive automatic processing was hypothesized to be found in patients with PD, as indexed by enhanced MMNs.

2. Method

2.1. Participants

Fifteen patients with PD (eight females, all right-handed) and 15 age- and gender-matched healthy volunteers (nine females, one left-handed) with an age range of 18–60 years participated. The patients were recruited from the First Affiliated Hospital of Dalian Medical University. The structured clinical interview for DSM-IV was performed for diagnostic purposes (First, Spitzer, Gibbon, & Williams, 1995). All patients met the DSM-IV criteria for PD with or without agoraphobia (two patients had agoraphobia). The patients were not taking antidepressants, antipsychotics, anxiolytics, or hypnotics and were not receiving ongoing psychotherapy. The healthy control subjects had no history of any psychiatric disorder or major physical illness and were not taking any medication known to affect the central nervous system. The exclusion criteria for both groups included psychiatric or neurological illness, severe brain injury, concurrent alcohol or drug abuse, and hearing or sight impairments. Patients and normal healthy participants were required to complete the 14-item Hamilton anxiety rating scale (HAMA-14) and the mini-mental state examination to evaluate the severity of their anxiety and dementia, respectively. The patients also completed the panic disorder severity scale (PDSS) (Argyle et al., 1991), which is a seven-item scale designed to assess the overall severity of PD symptoms. A summary of the demographics and symptom severity scores of both groups is presented in Table 1. The Institutional Review Board of Dalian Medical University approved this study. All participants signed consent forms prior to the study.

2.2. Stimuli and procedure

The multi-feature paradigm ("Optimum-1" paradigm) (Näätänen et al., 2004), which enables recording of MMNs from five different deviant stimuli at the same time, was used. In this paradigm, the stimuli are complex harmonic sounds composed of three sinusoidal partials: 500, 1000, and 1500 Hz. Note that the intensity of the 1000 and 1500 Hz partials were lower than that of the 500 Hz by 3 and 6 dB, respectively. A standard tone was applied binaurally at 60 dB above the individual subject's hearing threshold for a duration of 75 ms (including 5 ms of rise and fall).

The paradigm included five deviant tones that differed from standard tones. The specific deviant parameters were as follows: (1) frequency: half of the frequency deviants are 10% higher (composed of 550, 1100, and 1650 Hz partials), and the other half are 10% lower (450, 900, and 1350 Hz partials); (2) intensity: half of the intensity deviants are 10 dB higher, and the other half are 10 dB lower; (3) location: half of the location deviants have a spatial location of 90° to the right, and the other half have a 90° location to the left of the midline by introducing an interaural time difference of 800 us; (4) duration: 25 ms only; and (5) gap: removal of 7 ms (including 1 ms rise and fall) from the middle of the standard stimulus. The deviants were identical to the standards except where stated.

According to Näätänen et al. (2004), all deviant stimuli were presented in the same stimulus block. The presentation began with 15 standard tones that formed a memory trace for the tone, followed by a sequence in which every second tone was a standard (50%) and every other tone was one of the five deviants (10% each). Each deviant category was presented once every five deviants, and two deviants of the same category were never presented consecutively. Stimuli were presented at a stimulus onset asynchrony of 500 ms in three 5 min sequences (1845 stimuli in total), with a total recording time of 15 min for the five types of deviants. The participants were seated in a comfortable chair in a sound-attenuated and electrically shielded room. They were instructed to watch a silent movie and were asked to ignore the sound stimulus.

2.3. Electroencephalogram (EEG) recording and analysis

EEGs were continuously recorded (band pass 0.1–100 Hz, sampling rate 500 Hz) with a Neuroscan SynAmps2 amplifier using a