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Mismatch negativity in treatment-resistant depression and borderline personality disorder

Wei He [a,b], Hao Chai [a,b], Leilei Zheng [b,c], Wenjun Yu [a,b], Wanzhen Chen [a,b], Jianming Li [d], Wei Chen [a], Wei Wang [a,b,*]

[a] Department of Psychiatry, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China
[b] Department of Clinical Psychology, Zhejiang University School of Medicine, Hangzhou, China
[c] Department of Psychiatry, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
[d] Department of Clinical Psychology, Coal Mine Medical College of Northern China, Tangshan, China

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ABSTRACT

Objective: Cognitive dysfunctions, such as attentional impairment, are central features of both treatment-resistant depression (TRD) and borderline personality disorder (BPD). The treatment failure of TRD due to its comorbidity with BPD is debated in the literature. The mismatch negativity (MMN) of the event-related potentials provides an objective marker of involuntary stimulus selective processing, which might help shed light on this issue and provide an avenue for investigating a possible endophenotypic marker for TRD.
Method: We investigated MMN in 22 patients with TRD, 19 with BPD, and 22 with TRD cormorbid with BPD (TRD + BPD), as well as in 32 healthy volunteers, by employing an acoustic frequency deviance paradigm. In addition, we measured the depressive mood using the Plutchik–van Praag (PVP) depression inventory.
Results: There was no significant between-group difference for the N1 latencies/amplitudes, both to the standard and deviant stimuli, and no significant between-group difference for MMN latencies. However, MMN amplitudes were higher in the TRD group than those in the other three groups. PVP scores were highest in TRD + BPD, then TRD, BPD patients, and lowest in healthy subjects. The higher MMN was not correlated with PVP score, nor with the duration of life-long depression, which can be considered as a neurophysiological marker for TRD.
Conclusion: An atypical lack of inhibition on the irrelevant stimuli or increased cortical neuronal activity, especially frontal area, or both, might be responsible for the finding.

1. Introduction

Cognitive dysfunctions including disturbances in attention, learning, memory, and executive functions are central features of depression (Austin et al., 2001; Shenal et al., 2003), borderline personality disorder (BPD) (Posner et al., 2002; Ruocco, 2005), and BPD cormorbid with depression (Kurtz and Morey, 1999; Keilp et al., 2007). Treatment-resistant depression (TRD) is a more severe form of depression, characterized by a failure to respond either to meditation or to some forms of psychotherapy (Fava, 2003; Dunner et al., 2006; Berlim and Turecki, 2007). In order to clarify the treatment resistance in TRD, many investigators have explored the interface between depression and personality disorders (Mulder, 2002; Stanley and Wilson, 2006), since the latter respond poorly either to pharmacotherapy or to some forms of psychotherapy (Livesely, 2005; Sotsky et al., 2006). BPD in particular frequently presents as depressive mood (Zanarini et al., 2004; Levy et al., 2007) and some BPD typical characteristics, such as aggression or impulsivity (Links et al., 2008), increase the number and severity of suicidal attempts in those with a depressive disorder (Soloff et al., 2000; Brodsky et al., 2001). In addition, clinical investigations have shown that the changes (improvement or worsening) of either major depressive disorder (MDD) or BPD predicted changes in the other, although it was stronger for BPD's effect on MDD (Shea et al., 2004; Gunderson et al., 2004). Therefore, the identification of abnormal cognitive functions in TRD and BPD could add to our understanding of these two disorders.

Information processing impairments underlying these cognitive dysfunctions can be examined noninvasively by event-related potentials (ERPs). For instance, an ERP component, P3 (P3b or P300) elicited by the classical oddball task has often been reported to be reduced and delayed in MDD patients (Karaaslan et al., 2003; Urretavizcaya et al., 2003), or with BPD (Blackwood et al., 1986; Kutcher et al., 1987; Ruchsow et al., 2008). This result suggests abnormalities of active

Abbreviations: BPD, borderline personality disorder; ERP, event-related potential; MDD, major depressive disorder; MMN, mismatch negativity; PVP, the Plutchik–van Praag depression inventory; TRD, treatment-resistant depression.

* Corresponding author. Department of Clinical Psychology, Zhejiang University School of Medicine, Yuhangtang Road 388, Hangzhou, Zhejiang 310058, China. Tel.: +86 571 88208188.
E-mail addresses: wangmufan@msn.com, DrWang@Doctor.com (W. Wang).

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attention in these patients. Besides a reduced P3, Kemp et al. (2009, in press) found an exaggeration of both non-target and target P2 with a subsequent reduced P3 in depression. The abnormal P2, which indicates an over-processing of relevant and irrelevant stimuli, may reflect atypical inhibition of sensory input from further processing by an automatic mechanism crucial for early stimulus discrimination. The P2 variation might also contribute to the later ERPs such as P3, and P3 itself is vulnerable to motivational factors and task involvement of the participants. Therefore, P3 abnormalities in patients with depression or personality disorders are difficult to interpret to some extent.

On the other hand, mismatch negativity (MMN), an earlier ERP component, which does not require participants to be stimulus focused, is much less likely to be contaminated by motivational factors, and the significance of MMN results seem to be more useful in evaluating the information processing dysfunctions in MDD or in other psychiatric diseases (Picton et al., 2000; Näätänen et al., 2007). MMN in an auditory modality, which is elicited approximately 100–250 ms after the onset of deviant acoustic stimuli (e.g., with differences in frequency, duration, intensity, or inter-stimulus interval.), has been the most extensively employed index of involuntary preattentive function (Näätänen et al., 1978, 2007; Garrido et al., 2009). The supratemporal area and frontal lobe are both involved in the generation of MMN, and related neurotransmitters that mediate its generation are glutamate, GABA, dopamine, and 5-HT (Näätänen et al., 2007; Garrido et al., 2009).

The most promising clinical investigations of MMN are in schizophrenia which have shown a significant reduction of MMN (Garrido et al., 2009). A meta-analysis has confirmed that the decreased MMN is a robust feature of chronic schizophrenia which represents an underlying mechanism of attention impairment (Umbricht and Krljes, 2005). There have been, however, few studies investigating MMN in other neuropsychiatric disorders such as MDD, and the results to date remain controversial. Umbricht et al. (2003) examined both duration and frequency deviance-elicited MMN in MDD, together with schizophrenia and bipolar disorder and found a normal MMN in MDD. Lepistö et al. (2004) employed a syllable deviance and found unchanged MMN amplitude but shorter MMN latency in children with MDD. Recently, Kähkönen et al. (2007) found that the frequency MMN amplitude was increased in MDD patients. Moreover, Takei et al. (2009) found that the magnetic global field power of MMNm, a magnetic counterpart of MMN, was significantly smaller in MDD. These investigations, although reached inclusive results, might indicate a preattentive dysfunction in this disorder. Currently, there is no MMN data available in patients with BPD, but it was found that high-impulsive individuals have shown a larger frequency MMN than low-impulsive individuals (Franken et al., 2005).

Our study was designed to answer the following questions: Firstly, would MMN morphology in TRD be the same as that reported in MDD? Secondly, would MMN be larger in BPD as in those with high levels of impulsivity? Thirdly, would the changes of MMN in BPD contribute to those in TRD, or would the comorbidity of TRD and BPD (TRD + BPD) display a more severe deficit in information processing which could be reflected by MMN? In regard to the neurophysiological findings, the detection of frequency and duration changes of acoustic stimuli by brain neurons might be different (Kraus et al., 1994a,b), and the frequency deviance produces better and more reliable MMN than duration deviance (Jemel et al., 2002). Thus, we designed to assess the frequency MMN in healthy volunteers, patients with TRD, BPD, and TRD + BPD. We also employed the Plutchik–van Praag depression inventory (PVP, Plutchik and van Praag, 1987) to measure the depressive mood. With regard to the reported pre-attentive problems in psychiatric patients, such as, a larger MMN in high-impulsive subjects (Franken et al., 2005) and a smaller MMN in MDD patients (Gene Cos et al., 1999; Takei et al., 2009), we hypothesized that the frequency MMN would be larger in BPD and TRD + BPD, but smaller in TRD patients.

2. Method

2.1. Subjects

This investigation was carried out on 95 subjects, all of whom had to be drug or alcohol free for at least 72 h prior to testing. Each subject gave written informed consent to participate. Thirty-two healthy volunteers (15 females; mean age: 28.38 years ± 10.37 S.D.; range: 18–62 years) were recruited from students, hospital staff and paid volunteers from the general population. Nineteen outpatients were diagnosed as suffering from BPD (14 females; mean age: 31.63 ± 12.32; range: 18–55) according to the DSM-IV-TR criteria (American Psychiatric Association, 2000). Twenty-two outpatients were diagnosed as suffering from TRD (11 females; mean age: 25.05 ± 7.60; range: 18–41) using the following items: (1) symptoms met criteria for MDD according to DSM-IV-TR; (2) remission failed following the treatment of at least two usual antidepressants; (3) scored more than 25 on PVP (described below); (4) without psychotic diseases or drug abuse. Twenty-two patients were diagnosed as suffering from both TRD and BPD (TRD + BPD, 17 females; mean age: 27.27 ± 10.10; range: 18–55). All patients were diagnosed by three psychiatrists of our co-authors (WW, WC, and JML).

A semi-structured interview was conducted with each healthy subject in order to ascertain that they were not suffering or had not suffered from any psychiatric problems, including other types of personality disorder. In addition, patients did not have any brain lesions as determined using computerized tomographic or magnetic resonance imaging scans. About 50% of patients had received anxiolytics, antidepressants, or mood stabilizers before presenting to the clinic. The duration of life-long depression in patients with TRD or TRD + BPD was 3 to 10 years (mean 5.4 years). There was no significant age (one-way ANOVA, main effect, $F_{(3,\ 91)} = 1.48$, $p = .23$, MSE = 152.92), or gender (Pearson's chi-square with Yates correction, $\chi^2 = 6.81$, df = 3, $p = .08$) difference between different groups.

2.2. The Plutchik–van Praag depression inventory (PVP)

Each item of the 34-item PVP has three scale points (0, 1, 2) corresponding with increasing depressive tendencies. Subjects have "possible depression" if they score between 20 and 25, or "depression" if they score above 25 (Plutchik and van Praag, 1987). According to a recent study (Wang et al., 2002), the internal reliability of the inventory was .94 in a Chinese sample.

2.3. Stimuli and recording parameters

Subjects were seated in an armchair in a quiet room. Binaural tone stimuli of 80 dB SPL (50 ms in duration; rise/fall times of 5 ms) were delivered through headphones at an inter-stimulus interval of .625 s (1.6 Hz). The frequencies of frequent (90%) and deviant (10%) tones were 1.1 kHz and 1.2 kHz, respectively. These stimuli were presented in a randomized order. When compared to our study, others used either higher (Michie et al., 2000), lower (Sato et al., 2002), or similar (Umbricht et al., 2003) frequencies. With a pen in their dominant hand, subjects were instructed to arrange series of seven randomized digits (selected from 0 to 9) in an ascending order. This approach was chosen to keep attention away from the auditory stimuli.

Although both frontal and temporal generators contribute to MMN morphology, some studies showed that MMN amplitudes are reduced at the midline electrodes, including Fz, Cz and Pz, but not at mastoid sites (Sato et al., 2002; Baldeweg et al., 2004). Moreover, because of our limited number of amplifier channels, we recorded ERPs with cup electrodes placed at Fz, Cz, and Pz according to the 10–20 System. An earlobe reference was used (Näätänen et al., 1993; Micheyl et al., 2003) and a ground electrode was fixed to one arm. Electrode impedance was kept at <10 kΩ. All recordings were made on a Nihon Kohden Neuropack-sigma device using a band-pass of .01–30 Hz, and