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Research report

Neurophysiological handover from MMN to P3a in first-episode and recurrent major depression

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ABSTRACT

Background: Mismatch negativity (MMN) and P3a components are sequential and co-occur. MMN represents the pre-attentive index of deviance detection and P3a represents the attention orienting response. Major depressive disorder (MDD) is characterized by impaired pre-attentive information processing. To assess whether impaired pre-attentive information processing can lead to an impairment of subsequent orienting process as the neurophysiological transmission spreads from MMN to P3a in MDD.
Methods: MMN/P3a was obtained during a two-tone auditory paradigm with 8% duration deviants in 45 first-episode major depression subjects (F-MD), 40 recurrent major depression subjects (R-MD), and 46 healthy controls (HC).
Results: Compared with HC, F-MD and R-MD had lower MMN amplitudes and no differences were found between F-MD and R-MD. Notably, R-MD had lower P3a amplitudes and longer P3a latencies compared to HC, while F-MD had no differences. Interestingly, no correlations were found between the severity of depression and the deficits of MMN amplitude. The deficits of P3a amplitude, however, were negatively correlated with the severity of depression in F-MD and R-MD. Furthermore, the P3a amplitude deficits were positively correlated with the number of episodes in R-MD.
Limitations: Patients were on antidepressant medication.
Conclusions: The recurrence of depressive episodes can lead to impaired pre-attentive information processing, causing an impairment of subsequent orienting process as the neurophysiological transmission from MMN to P3a. It further suggests that the impaired processing indexed by MMN amplitude may be a stable trait biomarker for the appearance of depression, while P3a amplitude can be used a potential biomarker for recurrence.

1. Introduction

Major depressive disorder (MDD) is a common mental disease characterized by depressed mood, psychomotor retardation and bradyphrenia (American Psychiatric Association, 1994). Neuropsychological studies have indicated that MDD is related to multi-domain cognitive impairment, which includes memory function, mental imagery, attention span, working memory executive function, and perceptual speed (Castaneda et al., 2008; Chen et al., 2014b; Chen et al., 2013a; Chen et al., 2013b; Hammar, 2003; Hammar and Ardal, 2009).

Event-related evoked potential (ERP) has been utilized to probe individuals' processing of different cognitive strategies (Kim et al., 2013). The mismatch negativity (MMN) and P300, or P3, components are widely considered to be neurophysiological biomarkers for MDD (Kaur et al., 2011; Takei et al., 2009). MMN and P3 components tend to be measured using two independent experimental paradigms. MMN is measured under unconscious conditions, and P3 is measured under active conditions with task requirements (e.g. counting). However, several previous studies have reported that both MMN and P3 components can be simultaneously acquired in a passive oddball experimental paradigm (Ford and Mathalon, 2012; Kalechstein et al., 2009). MMN and P3a are sequential and coexist. The MMN is followed by the P3a component that is caused by

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stimulus driven fronto-central activity associated with attention orienting during task processing. This is thought to be different from the traditional P3b that derives from temporal–parietal activity related to contextual updating and subsequent memory storage (Polich, 2007). Therefore, the combination of MMN and P3 has been widely considered as the "MMN/P3a complex" (Hermens et al., 2010; Mager et al., 2005). The negative MMN component is generated by the frontal and temporal brain and reflects a neurophysiological mismatch between perceptual inputs and preceding sensory information that is stored in short-term memory trace (Naatanen et al., 2007). The positive P3a component, which is generated fronto-centrally, represents a subsequent attention orienting process that is induced after the detection of novel stimuli (Kalechstein (Kalechstein et al., 2009; Light et al., 2007; Polich, 2007). Previous studies have shown the neurophysiological transmission from MMN to P3a, where the former is a pre-attentive index of novel detection and the latter is the involuntary capture of attention (Friedman et al., 2001). Furthermore, several studies have demonstrated that both MMN and P3a amplitudes are related to cognitive and psychosocial function (Hermens et al., 2010; Kaur et al., 2012; Kaur et al., 2011; Naismith et al., 2012). This could mean that the MMN/P3a complex is a potential index of the fundamental perceptual and pre-attentive processing in the auditory pathway. Corresponding evidence suggests that the MMN/P3a complex is robust and is an ideal brain marker to assess cortical markers of the underlying neurobiology of MDD.

Recently, data from several MMN studies have shown that MDD patients have increased auditory MMN amplitudes (Kahkonen et al., 2007), reduced mean MMN amplitudes at temporal sites (Naismith et al., 2012) decreased MMN amplitudes and delayed MMN latencies at the fronto-central site (Qiao et al., 2013). These findings consistently suggest that MDD is impaired in pre-attentive information processing. Recently, several neuroimaging studies have indicated that altered striatal connectivity may correspond to the number of depressive episodes, thereby contributing to depressive recurrence risk and larger amygdala volumes of F-MD (Frodl et al., 2003; Meng et al., 2014). Furthermore, previous studies have demonstrated that R-MD presents a more serious cognitive impairment than F-MD in areas such as verbal memory performance, executive function, and mental representation processing (Chen et al., 2013a; Chen et al., 2013b; Fossati et al., 2004; Karabekiroglu et al., 2010). Corresponding evidence from these studies suggests that R-MD is a more serious impairment compared to F-MD, and the recurrence of depressive episodes may reinforce the extent of damage severity. However, very little is known about whether impaired pre-attentive information processing can spread to a subsequent orienting process and whether there is a difference regarding the underlying mechanism of neurophysiological transmission from the MMN to the P3a between F-MD and R-MD.

The objective of the current study was thus to investigate whether impaired pre-attentive information processing would spread to the subsequent orienting process as the neurophysiological transmission travels from MMN to P3a in the auditory pathways in F-MD and R-MD. Based on previous studies (Friedman et al., 2001; Kalechstein et al., 2009; Light et al., 2007; Polich, 2007), we predict that the impaired pre-attentive information processing will change to a subsequent orienting process as the neurophysiological transmission moves from MMN to P3a in MDD. Moreover, we predict that F-MD and R-MD will present with distinct impaired MMN/P3a profiles.

2. Materials and methods

2.1. Subjects

From inpatients (all of whom were Chinese Han and right-handed) at Center for Mental disease Control and Prevention of Baoji Third Hospital of the People's Liberation Army in China, we recruited 45 first episode major depression (F-MD, 21 males and 24 females) and 40 recurrent major depression (R-MD, 18 males and 22 females). Psychiatric diagnoses were made using a structured clinical interview (SCID). At least two psychiatrists agreed on a diagnosis based on the on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for melancholic MDD (American Psychiatric Association, 1994). The duration of illness ranged from 6 month to 20 years. Years of education ranged from 8 years to 22 years (Table 1). The severity of depression was evaluated using the 17-item Chinese Hamilton Depression Rating Scale ($HDRS_{17}$) scores with a minimum score of 22 needed to participate (Zheng et al., 1988). All patients received the same antidepressant medication (serotoninergic antidepressant) and the same psychological treatment (psychotherapic interviews and group therapy), and were clinically stable at the time of testing. Exclusion criteria for all patients was serious suicide risk, non-melancholic MDD (6 non-melancholic MDD were excluded in the present study), MDD with postpartum onset, bipolar disorder, comorbid Axis I diagnosis, history of substantial head injury, seizures, neurological diseases, dementia, impaired thyroid function, corticoid use or alcohol or substance abuse or dependence.

For comparison, subjects without any history of psychiatric illness were matched by to both F-MD and R-MD patients according to age, gender, and education (Table 1). The patients and control subjects gave their written informed consent after having received instructions concerning the experimental procedure. The Human Participants Ethics Committee of Baoji Third Hospital of the People's Liberation Army approved all procedures.

2.2. Neuropsychological assessment

General cognitive function was assessed by mini-mental state examination (MMSE). Moreover, a neuropsychological battery covering episodic memory, visuospatial function, information processing speed, attentional switching, and executive domains was utilized, comprising auditory verbal learning test-20 min delay recall (AVLT-20 min DR), trail making test-A and B (TMT-A and TMT-B), symbol digit modalities test (SDMT), clock drawing test (CDT), and digital span test (DST).

2.3. Procedures

After preparation for EEG recording participants were presented, through headphones, with 2500 binaural pure tones (1000 Hz, 75 dB SPL, 10 ms rise/fall) at a 500 ms stimulus onset asynchrony; this comprised a pseudo-random sequence of 2300 (92%) 50 ms standard tones and 200 (8%) 100 ms deviant tones (Naismith et al., 2012). Tones were presented while participants watched silent video of a comedy movie (and were asked to report back the storyline of the movie at the end of the task).

2.4. EEG acquisition and analysis

Electroencephalogram (EEG) measurements of 32 scalp locations based on the 10–20 system were recorded using a BrainAmp MR portable ERP system (Brain Products GmbH; Munich, Germany). Data were referenced to the nose. The eye movement artifact was monitored by recording vertical and horizontal electro-oculogram from sites above and below the midpoint of the left eye and on the outer canthus of each eye. Eye blink artifacts were corrected using the Semlitsch et al. (1986) method. The EEG was band-pass filtered from 0.1 to 100 Hz (and a gain of 20,000). In offline analyses, the EEG was band-pass filtered 0.01–30 Hz (Chen et al., 2014a; Chen et al., 2014b). EEG signal was analyzed with Brain Vision Analyzer software (Brain Products GmbH; Munich, Germany). EEG signals with amplitude larger than