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Research paper

Deficits of perceived spatial separation-induced prepulse inhibition in patients with bipolar disorder compared to healthy controls

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ABSTRACT

Objective: This study aimed to assess sensorimotor gating deficits in patients with bipolar disorder (BD) using a modified perceived spatial separation-induced prepulse inhibition (PSS-PPI) paradigm. The relationships between PSS-PPI, demographic and clinical characteristics, and cognitive functioning were also analyzed.

Methods: In this cross-sectional study, 30 patients with BD were compared to 33 healthy controls (HC) with respect to prepulse inhibition measures of PSS-PPI using a 120 ms lead interval. The Young Mania Rating Scale, Hamilton Depression Scale, and Hamilton Anxiety Scale were used to assess manic, depressive, and anxiety symptoms. Cognition was evaluated using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Stroop color-word test.

Results: Compared with HC, patients with BD had a lower PSS-PPI level. PSS-PPI showed medium effect size (ES) between patients with BD and HC (ES = 0.65). Among patients with BD, PSS-PPI was positively correlated with the language domain of RBANS and negatively correlated with double word time and color interference time. There were no differences in PSS-PPI levels between patients with and without psychotic symptoms or between those euthymic patients or depressive patients with BD.

Conclusions: Patients with BD show a sensorimotor gating deficit as measured by perceived spatial separation-induced PPI of the startle response, which was more sensitive compared to the classic PPI paradigm. Euthymic bipolar patients and depressive bipolar patients show similar PPI level. PPI deficit in patients with BD is related to cognition, but not with demographic and clinical characteristics.

1. Introduction

Sensory gating (SG) is a normal brain function used to filter out irrelevant stimuli. Defects to SG can lead to irrelevant stimuli flooding (Oranje et al., 1999; Ringel et al., 2004). The prepulse inhibition (PPI) of the startle reflex can be used as a neurobiological measure for exploring SG and early information processing (Cadenhead et al., 1999). In humans, the startle reflex is the rapid twitch of facial muscles induced by an intense, unexpected stimulus (e.g., acoustic stimulus) (Koch, 1999), that can be measured by eye blinks using electromyography (EMG) to detect orbicularis oculi muscles contractions. PPI manifests as a reliable reduction in the blink reflex amplitude component of the startle reflex (the pulse) if it is preceded for 30 to 300 ms by a weaker non-startling acoustic stimulus (the prepulse) (Kumari and Sharma, 2002).

PPI is deficient in several mental disorders, including schizophrenia, bipolar disorder (BD), obsessive-compulsive disorder (Swerdlow et al., 1993), attention deficit hyperactivity disorder (Ornitz et al., 1992), Tourette's disorder (Castellanos et al., 1996), and Huntington's disease (Swerdlow et al., 1995). PPI deficits were first demonstrated in patients with schizophrenia in 1978 (Braff et al., 1978) and have been studied primarily in patients with schizophrenia spectrum disorders. There is increasing evidence that patients with BD also have impaired PPI. Functional magnetic resonance imaging shows that reduced PPI is associated with lower response in the cortical-striatal-pallidal-thalamic circuit (Kumari et al., 2003). This region is associated primarily with

Abbreviations: BD, bipolar disorder; ES, effect size; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; HC, healthy controls; IQ, intelligence quotient; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; YMRS, Young Mania Rating Scale

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information filtering; depressive episodes are associated with deficits in filtering depressive thoughts and manic episodes with deficits in filtering manic thoughts.

PPI, a neurobiologic marker of BD, has been studied extensively in patients with BD with conflicting results. PPI has been shown to be reduced in patients with BD and their unaffected siblings (Giakoumaki et al., 2007; Sanchez-Morla et al., 2016). Pretty et al found PPI impairment in patients with BD and with acute psychotic mania (Perry et al., 2001). Carroll et al found no difference in PPI between patients with BD experiencing acute manic or mixed episodes (independent of psychotic symptoms) and HCs (Carroll et al., 2007), and Ivleva et al found no difference in PPI between psychotic outpatients with BD and healthy persons (Ivleva et al., 2014). In contrast, one study found that euthymic male patients with BD had decreased PPI (Gogos et al., 2009). Thus, it appears that PPI deficits are state-dependent (Barrett et al., 2005). Although most studies suggest that low PPI occurs more commonly in manic patients with psychotic symptoms, these mixed results are inconclusive and further studies should evaluate non-manic patients with BD.

An increasing number of studies show that participants who pay attention to prepulse stimulation have enhanced PPI (Cornwell et al., 2008; Heekeren et al., 2004; Thorne et al., 2005). Attentional modulation on PPI has been shown only at the 120 ms lead interval (Ashare et al., 2007; Dawson et al., 2000). The perceived spatial separation-induced PPI (PSS-PPI) paradigm is based on the precedence effect between a conditioned prepulse and background noise. Use of PSS-PPI with inter-stimulus intervals of 120 ms enhances the listener's ability to identify the target signal and further enhances PPI compared to perceived spatial co-location PPI (PSC-PPI).

Attentional deficits may greatly damage other cognitive functions, and a meta-analysis has suggested sustained attentional impairment in patients with BD (Bora et al., 2009; Dickinson et al., 2007; Fioravanti et al., 2005). The PPI deficit in patients with BD is related to emotional processing tasks (Sanchez-Morla et al., 2016). And some research have shown PPI to be associated with neurocognitive performance (e.g., working memory) (Kishi et al., 2012; Oliveras et al., 2015; Scholes and Martin-Iverson, 2009).

This study aimed to assess SG deficits in patients with BD using the PSS-PPI paradigm. Furthermore, we analyzed the relationship between PSS-PPI, demographic and clinical characteristics, and cognitive performance. We hypothesized that PSS-PPI would be a robust damage index and sensitive measure for specific cognitive variables in patients with BD.

2. Material and methods

2.1. Participants

This cross-sectional study was conducted at Beijing Anding Hospital, Capital Medical University, and study protocols were approved by the hospital's clinical research ethics committees. Assessments were conducted by qualified psychiatrists who were trained in methods ratings and scales.

Participants were enrolled from September 2014 to September 2016. Adult patients with a diagnosis of BD based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were eligible for the study. Diagnoses were made using the Structured Clinical Interview for DSM-IV Axis I disorders-Patient Edition (SCID-I/P) (First et al., 2002; Li et al., 2008). Patients had not received electric convulsive therapy within the preceding 3 months and the total score of Young Mania Rating Scale (YMRS) (Young et al., 1978) below 8. Participants were eligible for inclusion if they were aged 18 to 55 years, had 9 years or more of formal education, were non-smokers, had normal hearing. Healthy controls (HCs) recruited for this study had no history of BD or other mental disorder. Patients were excluded if there was a history of psychosis caused by a general medical condition, severe suicidal thoughts or attempts, smoking, drug dependence, or a major chronic medical or neurological condition. All participants provided written informed consent prior to enrollment.

2.2. Clinical assessment

Patients' sociodemographic characteristics and clinical data were collected using a questionnaire designed for the study. Mood status was assessed using the YMRS, Hamilton Depression Scale (HAM-D) (Hamilton, 1960; Zheng et al., 1988), and Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959; Tang, 1984). In patients with BD, psychotic symptom status was determined using the SCID for history and current episode.

2.3. Intelligence quotient

The Chinese version of the Wechsler Adult Intelligence Scale, revised (Wechsler, 1981) short form was used to evaluate intelligence quotient (IQ). The four included subsets for this evaluation were information, similarities, picture completion, and block design (Pang et al., 2011).

2.4. Cognitive performance assessment

Neurocognitive performance was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Stroop color-word test (Randolph, 1998; Stroop, 1935). The RBANS, which was developed in 1998 by Randolph, has been translated into multiple languages and validated in several countries, (Muntal Encinas et al., 2012; Wilk et al., 2002; Yamashima et al., 2002) including China (Zhang et al., 2008). The Chinese version of the RBANS has demonstrated good reliability and validity, and is easily performed in 30 minutes (Zhang et al., 2008).

RBANS consists of five domains (12 tests): attention (digital span, coding); language (picture naming, semantic fluency); visuospatial/constructional (figure copy, line orientation); immediate memory (list learning, story memory); and delayed memory (list recall, list recognition, story recall, figure recall). Each domain has a raw score that is corrected based on sex and age, using the RBANS table and converted to five cognitive domain scaled scores to be used in subsequent analyses. Raw scores for each domain are summed to yield a total score for overall cognitive function with a mean value of approximately 100 (standard deviation [SD] = 15).

The Chinese version of the Stroop color-word test consists of word, color, color interference, and word interference assessments (Stroop, 1935; Wang et al., 2008). Total time to completion and number of items completed correctly are measured for each section. The first task requires the participant to read the names of words written for colors in black ink. The second task is to read the names of colors of block written in colored ink. The third task (color interference effect part) is to read the names of words written in colored ink while ignoring the color of the printed words. The fourth task (word interference effect) is to say the color of the ink while ignoring the word written for colors. We determined the color and word interference time, which is the latency for naming all words and colors correctly in the third and fourth tasks minus the time needed of the first and second tasks.

2.5. Startle reflex measurements

Each participant sat in a recliner chair in a sound-attenuated room with suitable temperature and humidity and was kept awake during the trials. Participants were instructed to watch a black spot on a screen, try not to blink their eyes often. Participants were tested to ensure pure auditory threshold limits of 40 dB or less, with threshold differences between ears of 15 dB or less.

The background noise was set at 0 to 10 kHz, 60 dB sound pressure