



Research paper

Sexually dimorphic deficits of prepulse inhibition in patients with major depressive disorder and their relationship to symptoms: A large single ethnicity study

Junko Matsuo, Miho Ota, Shinsuke Hidese, Hiroaki Hori, Toshiya Teraishi, Ikki Ishida, Moeko Hiraishi, Hiroshi Kunugi*

Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

ARTICLE INFO

Keywords:

Prepulse inhibition
Major depressive disorder
Startle reflex
Habituation
Symptoms
Sex difference

ABSTRACT

Background: Sensorimotor gating deficits as measured by prepulse inhibition (PPI) of acoustic startle reflex have been repeatedly observed in patients with schizophrenia. However, studies investigating PPI in patients with major depressive disorder (MDD) are scarce, and this issue remains to be elucidated.

Methods: Subjects were 221 patients with MDD and 250 age-matched healthy comparison subjects. Depressive symptoms were assessed by the 21-item version of the Hamilton Depression Rating Scale (HAM-D21), and the scores were divided into six factors. Thirty-five trials of startle reflex to pulse alone and pulse with prepulse were measured by electromyography. Startle magnitude, habituation, and PPI were compared between patients and comparisons stratified by sex. Relationships of startle measures to symptoms and antidepressant medication were assessed.

Results: Male patients showed significantly reduced PPI compared to male comparisons, while no significant PPI difference was found between female patients and comparisons. HAM-D21 total score and several subscales were significantly correlated with PPI only in male patients. The effect of antidepressant medication was not significant for either male or female patients.

Limitations: Possible effects of the menstrual cycle could not be excluded among female subjects.

Conclusions: These findings suggest that male patients with MDD show sensorimotor gating deficits in a state-dependent manner. However, we obtained no evidence for such abnormalities in female patients with MDD.

1. Introduction

Prepulse inhibition (PPI), defined as the reduction startle reflex due to weak sensory prestimulation, is a neurophysiological measure of sensorimotor gating. PPI deficits in patients with schizophrenia were first reported by Braff and colleagues (Braff et al., 1978), and their findings have been replicated by a number of studies involving subjects across various ethnicities (Braff et al., 2001) including our own studies on a Japanese population (Kunugi et al., 2007; Matsuo et al., 2016). Such deficits were reported in patients with multiple neuropsychiatric disorders characterized by inhibitory deficits of sensory, motor, and cognitive functions, such as schizophrenia spectrum disorder, bipolar disorders at least in the psychotic manic phase, obsessive-compulsive disorder, and Tourette's syndrome, although the results were inconsistent as to the presence of PPI deficits among studies (Braff et al., 2001; Kohl et al., 2013). Common abnormalities in the cortico-striato-pallido-pontine (CSPP) and/or cortico-striato-pallido-thalamic (CSPT)

circuitries are considered to be involved in the pathophysiology of these disorders and the modulation of PPI (Braff et al., 2001; Swerdlow et al., 1992). Subsequent brain imaging studies have supported this hypothesis demonstrating that PPI was associated with activation in areas such as pons, striatum, hippocampus, thalamus, and frontal and parietal cortical regions (Takahashi et al., 2011).

Compared to patients with schizophrenia, PPI in patients with major depressive disorder (MDD) has been less studied (Kohl et al., 2013). The first study on sensorimotor gating was conducted by Taiminen et al., who assessed the habituation of startle reflex in patients with psychotic and non-psychotic depression and compared it with that in patients with schizophrenia and controls. They found that both patients with psychotic depression and schizophrenia had reduced habituation when compared to controls and patients with non-psychotic depression, although no significant difference was reported between patients with psychotic and non-psychotic depression (Taiminen et al., 2000). Subsequently, three studies examined PPI in

* Corresponding author.

E-mail address: hkunugi@ncnp.go.jp (H. Kunugi).

patients with non-psychotic depression and all these studies reported that the patients did not have PPI deficits when compared to controls, although Perry et al. found a moderate effect size of difference (Cohen's $d=0.63$) between the severely-depressed MDD and non-patient group (Ludewig and Ludewig, 2003; Perry et al., 2004; Quednow et al., 2006). In contrast, one recent study examined PPI in postpartum women and found that depressed postpartum women showed significantly lower PPI than those without depression (Comasco et al., 2016). Since all these studies were conducted with a small sample size, studies with a larger sample size are necessary. Given that patients with MDD have abnormalities in CSPT circuits (Bora et al., 2012; Kong et al., 2013; Koolschijn et al., 2009; Price and Drevets, 2012), it is possible that they may show deficits in PPI.

When assessing PPI, it is important to consider the existence of sex difference in PPI (men > women) (Abel et al., 1998; V. Kumari, 2011; Swerdlow et al., 1997, 1993). In this context, comparison groups should be matched for sex with patient groups; or more preferably, group comparison should be stratified by sex. In addition to sex, there are other factors that were reported to have influence on PPI such as age (Ellwanger et al., 2003; Ludewig et al., 2003; Swerdlow et al., 1995), ethnicity (Swerdlow et al., 2005), and smoking status (Della Casa et al., 1994; Duncan et al., 2001; Kumari and Gray, 1999; Swerdlow et al., 2006). Ethnic differences in startle magnitude and PPI were reported between Caucasians and Asians, with Asians having lower startle magnitude and higher PPI compared to Caucasians (Swerdlow et al., 2014, 2007, 2005).

Thus, we tested for startle measures in a large number of patients diagnosed as MDD and compared their PPI to that of age-matched healthy comparison subjects. This study has advantages such that all subjects were of a single ethnicity (Japanese) and that the analyses were performed men and women separately. The aim of this study was (1) to examine whether startle and its modifications are in fact impaired in patients with MDD and (2) to see whether such impairments, if any, are related with depression severity and antidepressant medication. Considering that MDD patients are clinically observed to have difficulty in suppressing intrusive negative thoughts, we hypothesized that PPI deficits would exist in patients with MDD having severe depressive symptoms. To test this hypothesis, we made a stratified analysis based on depression severity. As to the effect of antidepressant medication, previous studies showed no clear effects on PPI in either humans or animals (Brafk et al., 2001). Therefore, we hypothesized that there would be no significant difference in PPI between patients with and without antidepressant medication.

2. Methods

2.1. Subjects

Subjects were 221 Japanese patients with MDD (106 men and 115 women) and 250 Japanese healthy comparisons subjects (116 men and 134 women) aged 18–64 years, who volunteered to participate in neurocognitive research studies between 2009 and 2016 at the National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan, through notices posted in the NCNP Hospital, website announcements, or advertisements in a local free magazine. The majority of the comparison subjects overlapped with our previous study (Matsuo et al., 2016).

Consensus diagnosis was made for each patient by at least two experienced psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 4thth edition (DSM-IV) (American Psychiatric Association, 2000) criteria based on detailed interviews and medical records, if available. Comparison subjects were screened using the Japanese version of the Mini-International Neuropsychiatric Interview (Otsubo et al., 2005; Sheehan et al., 1998) and further confirmed to have no history of psychiatric/neurological disorders, ongoing medical illness, or family history of psychosis within the

second degree relatives. Those individuals who had a confirmed diagnosis of intellectual disability, attention-deficit hyper-activity disorder, organic brain disorder, or panic disorder, and/or those with a current or past medical history of substance-related disorders or severe trauma were excluded. Pregnant or lactating women were not included. Those with hearing deficits as confirmed by audiometry (threshold: average hearing level of 500 Hz, 1000 Hz, and 2000 Hz to be < 40 dB) were also excluded. Depression severity was assessed using the 21-item version of the Hamilton Depression Rating Scale (HAM-D21) (Hamilton, 1967), in addition to the six-factor model proposed by Seretti et al. (1999) that includes the following: “core depressive symptoms” (items 1, 2, 7, 8, 10, 13); “sleep” (items 4, 5, 6); “activity” (items 7, 8); “psychotic anxiety” (items 9, 10); “somatic anxiety” (items 11, 12, 13); and “delusion” (items 2, 15, 20). Among the patients, 62 were remitted and 159 were unremitted patients, according to the consensus definition for remission (threshold: HAM-D17 < 8) proposed by Frank et al. (1991).

The study design was reviewed and approved by the National Center of Neurology and Psychiatry Ethics Committee. All subjects provided written informed consent after the nature of the procedures had been fully explained to them.

2.2. Startle reflex measurement

Diagnostic interview, assessment with HAM-D21, audiometry and PPI test were conducted on the same day. To avoid the effects of nicotine on PPI, subjects refrained from smoking for at least 30 min prior to testing (Kumari et al., 1996). A computerized Startle Reflex Test Unit for Humans (O'Hara Medical Co., Tokyo, Japan) was used, which delivered acoustic stimuli binaurally through headphones to the subject in a computerized startle paradigm, recorded and amplified the startle eye-blink electromyographic (EMG) reflexes from the orbicularis oculi muscle, digitized and collected on the computer. The procedures of bioelectrical measurement by electromyography have been detailed previously (Kunugi et al., 2007). A session comprised three blocks with a continuously presented background white noise (50 to 24,000 Hz) of 70 dB (A) starting 3 min prior to block 1. In block 1, the startle reflex of white noise of 115 dB (A) lasting for 40 ms to pulse alone (PA) trial was recorded five times; in block 2, the startle reflex to the same PA trial, or to pulse with four different conditions of prepulse trial (60 ms, 86 dB; 60 ms, 90 dB; 120 ms, 86 dB; 120 ms, 90 dB; white noise each lasting for 20 ms) was measured five times for each condition in a fixed pseudorandom order, making a total of 25 trials; and in block 3, startle reflex to the same PA trial was measured five times. Inter-trial intervals (15 s on average, range: 10–20 s) were randomly changed. The entire session consisted of a total of 35 trials, lasting approximately 15 min.

The startle measures examined were as follows: (1) mean PA startle magnitude in block 1, which we called basic startle reflex (BSR), (2) habituation (%), which is the attenuation of startle reflex to the repeated stimuli, calculated as the percent decrement in PA startle magnitude between block 1 and block 3, and (3) PPI (%), which is the attenuation of startle reflex that occurs when the startling stimulus is preceded by the weak prestimulus, calculated as the percent decrement in startle magnitude between PA and prepulse trials in block 2, as described previously.

Subjects were classified as non-responders if their BSR was < 0.05, and were excluded from further analyses based on our previous studies (Kunugi et al., 2007; Matsuo et al., 2016). Furthermore, individuals with startle magnitude ≤ 0.03 in PA trial in block 2 were also excluded for the analysis of PPI, since average startles less than these criteria were too small to calculate the valid percent of PPI. Thus, viable data for the PPI analysis was collected from 143 patients with MDD (74 men) and 189 comparison subjects (84 men), summing up 332 subjects in total (158 men).

Download English Version:

<https://daneshyari.com/en/article/5721907>

Download Persian Version:

<https://daneshyari.com/article/5721907>

[Daneshyari.com](https://daneshyari.com)