Journal of Psychiatric Research 82 (2016) 155–162

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

A large single ethnicity study of prepulse inhibition in schizophrenia: Separate analysis by sex focusing on effect of symptoms

Junko Matsuo, Miho Ota, Hiroaki Hori, Shinsuke Hidese, 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

Article history:
Received 25 March 2016
Received in revised form
13 July 2016
Accepted 29 July 2016

Keywords:
Prepulse inhibition
Habituation
Schizophrenia
Sex difference
Symptom

ABSTRACT

Deficits in sensorimotor gating, as measured with prepulse inhibition (PPI), have been considered an endophenotype of schizophrenia. However, the question remains whether these deficits are related to current symptoms. This single site study aimed to explore clinical features related to the modulation of startle reflex in a large sample of Japanese patients with schizophrenia (DSM-IV). The subjects comprised 181 patients and 250 healthy controls matched for age and sex. Schizophrenia symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS). Startle reflex to acoustic stimuli was recorded using a startle stimulus of 115 dB and a prepulse of four different conditions (intensity: 86 dB or 90 dB; lead interval: 60 ms or 120 ms). Patients exhibited significantly reduced startle magnitude ($p < 0.001$), habituation ($p = 0.001$), and PPI (90 dB, 60 ms, $p = 0.016$; 90 dB, 120 ms, $p = 0.001$) compared with controls. Patients of both sexes exhibited significantly lower habituation and PPI (90 dB, 120 ms) compared with the same sex controls. We could not detect a significant correlation with any clinical variable in the entire patients, however, when men and women were examined separately, there was a negative correlation with the PANSS cognitive domain ($\rho = -0.33$, $p = 0.008$) in men, but not in women. Moreover, when patients were subdivided into four clusters, two clusters with high positive symptoms showed significant PPI deficits in men. Our results suggest that sensorimotor gating is impaired in schizophrenia of both sexes, and PPI deficits may be related to thought disturbance and disorganization in male patients with schizophrenia.

1. Introduction

Sensorimotor gating is a preattentive, automatic process, involving control of motor responses to sensory stimuli, by which excess or trivial stimuli are screened or "gated out" of awareness, allowing for efficient processing of relevant information (Braff and Geyer, 1990). Prepulse inhibition (PPI) is an operational measure of this inhibitory function, defined as an attenuation of the startle reflex when the startle-eliciting stimulus, the pulse, is preceded by a weaker sensory stimulus, the prepulse (Graham, 1975). Oversensitivity to sensory stimulation theoretically correlates with stimulus overload and may lead to cognitive fragmentation (Braff and Geyer, 1990).

PPI deficits in schizophrenia were first reported by Braff and colleagues (Braff et al., 1978), and subsequently replicated by numerous studies across various ethnicities (Braff et al., 2001), including our own with a Japanese population (Kunugi et al., 2007). Further studies have also found such deficits in unaffected first-degree relatives of schizophrenia patients and in subjects with schizotypal personality disorder (Cadenhead et al., 2000; Kumari et al., 2005), which suggests that these deficits are a genetically transmitted fundamental trait, in other words, a promising endophenotype of schizophrenia (Braff and Light, 2005; Light et al., 2012).

A growing number of reports in the literature, however, have shown that PPI deficits in schizophrenia patients may be, at least partially, ameliorated by antipsychotic medication (Aggernaes et al., 2010; Kumari et al., 2002, 1999; Leumann et al., 2002; Oranje et al., 2002; Quednow et al., 2006; Swerdlow et al., 2014, 2006; Wynn et al., 2007). Interestingly, the difference in PPI between the medicated and unmedicated schizophrenia patients was

* Corresponding author. Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1, Ogawahigashi, Kodaira, Tokyo, 187-8502, Japan.
E-mail address: hkunugi@ncnp.go.jp (H. Kunugi).

http://dx.doi.org/10.1016/j.jpsychires.2016.07.026
0022-3956/

no longer significant when the severity of the positive syndrome was entered as a covariate (Weike et al., 2000). This finding was corroborated by a longitudinal study which reported that PPI deficits in medicated patients were observed in acute illness, but not in an improved clinical state, suggesting that PPI deficits may be state dependent (Meincke et al., 2004b). Another within-subject study suggested that improvements in sensorimotor gating may be related to antipsychotic-related symptom reduction, rather than the antipsychotic medication itself (Minassian et al., 2007). The effects of antipsychotics on PPI were not evident when patients with schizophrenia were acutely symptomatic (Xue et al., 2012).

So far, evidence linking PPI deficits to schizophrenia symptoms has been inconsistent (Braff et al., 2001). PPI deficits have been related to positive symptoms (Braff et al., 1999; Wang et al., 2013; Weike et al., 2000; Xue et al., 2012), negative symptoms (Braff et al., 1999; Xue et al., 2012), distractibility (Karper et al., 1996), thought disorder (Perry and Braff, 1994; Perry et al., 1999), formal thought disorder and bizarre behavior (Meincke et al., 2004b), psychological discomfort (Duncan et al., 2006), and general psychopathology (Martinez-Gras et al., 2009; Xue et al., 2012). Conversely, large cohort studies of schizophrenia patients (the Consortium on the Genetics of Schizophrenia: COGS) have found no association between PPI deficits and positive or negative symptoms (Swerdlow et al., 2014, 2006). However, subjects in these studies were on either limited to or dominantly males.

Sexual dimorphism of PPI in healthy adult subjects has been well documented, with men exhibiting higher PPI than women in the majority of studies (Abel et al., 1998; Swerdlow et al., 1999, 1993). However, fewer studies have examined the sex differences in schizophrenia patients, producing inconsistent findings. One study found no effect of sex on PPI (Ludewig et al., 2002), while another study reported that PPI deficits were detected only in men with schizophrenia (Kumari et al., 2004). On the contrary, there are also studies reporting significant PPI deficits in schizophrenia women compared with healthy women (Braff et al., 2005), and significantly lower PPI in schizophrenia women than men (Swerdlow et al., 2014, 2006).

Swerdlow and colleagues suggested that such “variability in the relationship between these clinical variables and PPI across studies may reflect site differences in patient characteristics or PPI methodology, and the intrinsic heterogeneity of schizophrenia” (Swerdlow et al., 2014). Indeed, most studies included various ethnicities that may have influenced the outcome, since ethnic differences in startle magnitude and PPI were reported (Swerdlow et al., 2014, 2007, 2005). Therefore, this single site study aimed to explore clinical features related to the modulation of startle reflex in a large sample of Japanese patients with schizophrenia. The advantages of this study are that all subjects were of a single ethnicity (Japanese), and that tests were administered with the same equipment in the same measurement room. Furthermore, in order to eliminate the factors that might have influenced PPI, diagnostic groups were matched for sex and age, and separate analyses were made on men and women. This is a replication of our preliminary study, where we employed a small independent sample and demonstrated PPI deficits in schizophrenia patients for the first time in Asian subjects (Kunugi et al., 2007). More specifically, we had two questions: 1) whether reduced startle reflex, habituation, and PPI were present in the patient group as a whole, and separately in men and women when compared with their respective healthy counterparts, and 2) whether PPI deficits were related to any schizophrenia symptoms/subgroups. We hypothesized that reduced startle measures would be observed in the patient group, in both men and women, and PPI deficits would be related to certain symptoms/subgroups.

2. Methods

2.1. Subjects

The subjects comprised 181 patients with schizophrenia and 250 healthy controls aged 18–64 years, matched for sex and age. All subjects were biologically unrelated Japanese individuals. Demographic and clinical data are presented in Tables 1 and 2, respectively. They were recruited over 6 years (2009–2015) by our research team 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 paper. Patients in acute psychosis were not enrolled.

Diagnosis of schizophrenia was made through the consensus of at least two experienced psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) (American Psychiatric Association, 2000) criteria, based on clinical interviews, and medical records, if available. Those individuals who had a concurrent confirmed diagnosis of intellectual disability, attention-deficit hyperactivity disorder, organic brain disorder, or those who had a current or past history of substance-related disorders were excluded. Controls were rigorously screened based on the Japanese version of the Mini-International Neuropsychiatric Interview (MINI) (Otsubo et al., 2005; Sheehan et al., 1998), and unstructured interviews in order to rule out axis I disorders as defined in the DSM-IV. Controls were also required to be physically and neurologically healthy, and have had no previous contact with psychiatric services, psychiatric medications, exposure to severe trauma which may lead to post-traumatic stress disorder, or any positive family history of psychosis (schizophrenia and bipolar disorder) and/or autism spectrum disorder (ASD) within a second-degree relative. An audiometer was used to exclude subjects with hearing deficits (threshold: average detection level at 500 Hz, 1000 Hz, and 2000 Hz to be < 40 dB).

Schizophrenia symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay and Fiszbein, 1987), which generates positive syndrome, negative syndrome, and general psychopathology. Symptomatology assessed by the PANSS was also evaluated by the five-factor model of schizophrenia (Lindenmayer et al., 1994) which consists of negative, positive, cognitive, depression/anxiety, and excitement domains. Daily dose of antipsychotics was calculated as chlorpromazine equivalents in mg/day according to published guidelines (Inada and Inagaki, 2015).

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study protocols were reviewed and approved by the NCNP Ethics Committee. All subjects provided written informed consent prior to their participation in the study after the nature of the procedures had been fully explained.

2.2. Startle reflex measurement

Subjects were asked to refrain from smoking for at least 30 min prior to testing, in order to avoid the effects of nicotine on PPI (Duncan et al., 2001; Hong et al., 2008; Kumari et al., 2001). They were sat comfortably in a recliner chair, in a sound-attenuated room. A computerized Startle Reflex Test Unit for Humans (O'Hara Medical Co., Tokyo, Japan) was used. Acoustic stimuli of white noise (50–24,000 Hz) were delivered binaurally through headphones to the subject in a computerized startle paradigm. Startle eye-blink magnitude was measured using electromyographic (EMG) recording from the orbicularis oculi muscle with two small electrodes positioned below and in line with the pupil of each eye, and a ground electrode behind each ear. Instruction to the subjects, the procedures of skin preparation for bioelectrical