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Acoustic startle response and its modulation in schizophrenia and autism spectrum disorder in Asian subjects

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ABSTRACT

The acoustic startle response (ASR) and its modulation, including prepulse inhibition (PPI), are considered to be promising neurophysiological indices for translational research in psychiatry. Impairment of the PPI has been reported in several psychiatric disorders, but particularly in schizophrenia, where PPI is considered to be a candidate endophenotype of the disorder. Although the profiles of the ASR differ between races, recent studies of single ethnicity samples in Asia were in accord with a number of studies from Western countries, in reporting that patients with schizophrenia exhibit impaired PPI.

The PPI of the ASR is known to develop before 8 years of age, and PPI impairment has only been reported in adults (not children) with autism spectrum disorder (ASD), which involves atypical features that are present from early development. Recent Asian studies of children with ASD suggest that comprehensive investigation of the ASR and its modulation, including the startle response to weak startle stimuli, peak startle latency, and PPI, may contribute to an understanding of the impairment of the neural circuitry in children with ASD and its comorbid behavioral problems.

In this review, we review recent findings on the ASR and its modulation from Asian countries, and discuss its potential use for studying sensorimotor gating and its relationship to schizophrenia and ASD.

In conclusion, the ASR and its modulation can provide a well-established global neurophysiological index for translational research in psychiatric disorders. Future studies investigating the development of sensorimotor gating in early development may contribute to prevention of psychiatric disorders.

1. Introduction

The acoustic startle response (ASR) and its modulation, including prepulse inhibition (PPI), are considered to be some of the most promising neurophysiological indices for translational research in psychiatry; research that combines both basic and clinical research for the purpose of understanding the complex pathogenesis of the genetic and environmental interactions underlying psychiatric disorders. As the ASR can be assessed using simple nonlinguistic stimuli, the ASR, and especially the related PPI, have been widely investigated across human races (Hasenkamp et al., 2008; Swerdlow et al., 2007, 2005) and other species (Powell et al., 2012, 2009; Swerdlow and Geyer, 1998; Swerdlow and Light, 2016) using similar experimental paradigms (Light and Swerdlow, 2014; Swerdlow and Light, 2016).

The ASR is a fast twitch of facial and body muscles in response to a sudden and intense sound (Koch, 1999). This response pattern suggests that the startle may have a role in protecting against injury from a predator or a blow, and is an element of the flight response. PPI is usually defined as a reduction in the startle reflex due to weak sensory prestimulation (Braff et al., 1978), and is the most commonly used psychophysiological index of sensorimotor gating, which is an autonomic inhibition system that regulates the motor response to sensory input. This inhibitory process has been proposed to contribute to the selective and efficient processing of relevant information.

Impairment of the PPI has been reported in several psychiatric disorders (Swerdlow et al., 2016; Takahashi et al., 2011), of which schizophrenia is the most prominent. Although the profile of the ASR differs across racial groups (Hasenkamp et al., 2008; Swerdlow et al., 2007, 2005), studies of both Asian and Caucasian subjects indicate that patients with schizophrenia exhibit impaired PPI, and that impaired sensorimotor gating may be a global common psychophysiological feature of schizophrenia.

Investigation of the ASR and its modulation in other neurodevelopmental disorders, such as autistic spectrum disorder (ASD; McAlonan et al., 2002; Ornitz et al., 1993; Perry et al., 2007;

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Takahashi et al., 2016; Yuhas et al., 2011) or Tourette's syndrome (Swerdlow, 2013; Swerdlow et al., 2001), may provide important insights into the underlying mechanism behind the developmental aspect of sensorimotor gating and its relationship to psychiatric disorders. In particular, ASD, which has atypical features from early development, is known to have a relatively high incidence (12–17%) of comorbid psychotic disorders, which manifest mainly in adults (Lai et al., 2014). Although the developmental timing of symptom onset clearly differs between schizophrenia and ASD, there are several similarities in their clinical presentation, including social dysfunction and sensory abnormalities (Konstantareas and Hewitt, 2001), as well as genetics (State and Levitt, 2011) and neurobiology (State and Sestan, 2012). Thus, basic investigation of the ASR and its modulation in children with ASD may provide deeper insight into the development of sensorimotor gating, which is related to psychotic disorders.

In this review, we review recent findings related to the PPI of the ASR in schizophrenia from a single ethnicity Asian country; findings that suggest that impaired sensorimotor gating is a global common psychophysiological feature of schizophrenia. We also review recent studies on ASR and its modulation in children with ASD; an area of research that is evolving in Asian countries, particularly for the purpose of forwarding the understanding of the developmental aspects of auditory sensory processing in relation to psychiatric disorders.

2. Prepulse inhibition of the ASR in Asian patients with schizophrenia

Schizophrenia is one of the most prominent psychiatric disorders presenting with deficits in PPI. Impaired sensorimotor gating has been considered to be a common psychophysiological feature of schizophrenia, which may theoretically lead to severe dysfunctions in perception, attention, and thinking (Braff and Geyer, 1990). Since the first report on their occurrence (Braff et al., 1978), reductions in PPI have been consistently demonstrated in patients with schizophrenia (Braff et al., 2001a, 2001b; Swerdlow et al., 2014, 2008), and recently, PPI has been considered a promising candidate endophenotype of schizophrenia (Braff et al., 2007; Braff and Light, 2005; Greenwood et al., 2007, 2016, 2013; Swerdlow et al., 2014; Turetsky et al., 2007).

Reduced PPI in patients with schizophrenia has also been consistently reported in recent studies on Asian subjects of single ethnicities (Kunugi et al., 2007; Moriwaki et al., 2009; Takahashi et al., 2008), despite the smaller magnitude of the ASR in Asian subjects in comparison to Caucasians (Swerdlow et al., 2007, 2005). Table 1 shows a summary of previous ASR studies of schizophrenia and related conditions in Asian populations. Most PPI studies on Asian subjects with schizophrenia have reported on single ethnicity Japanese patient samples. Firstly, a Japanese study of PPI in schizophrenia (Kunugi et al., 2007) examined the PPI of the ASR in 20 Japanese patients with chronic schizophrenia under antipsychotic medication, and compared it with that in 16 healthy Japanese controls matched for age and sex. The PPI differed significantly between the two groups. Later Japanese studies with relatively larger sample sizes (Kishi et al., 2012, 2013; Matsuo et al., 2016; Moriwaki et al., 2009; Takahashi et al., 2008) have also consistently reported a reduction of PPI in patients with schizophrenia (n: 51–181) in comparison with healthy controls (n: 55–250). Some of these studies also reported reduced habituation of the ASR in Japanese patients with schizophrenia (Matsuo et al., 2016; Moriwaki et al., 2009). Habituation is another ASR modulation that is usually defined as a decrease in the behavioral response after repeated presentation of an identical stimulus, which is not caused by sensory adaption or effector fatigue (Geyer and Braff, 1982). Reduced ASR habituation may reflect the impaired gating of repeated stimuli, and may result in cognitive disruption via sensory overload. Reduced PPI of the ASR in schizophrenia have also been observed in Chinese samples (Wang et al., 2012; Xue et al., 2012). In Chinese samples, PPI was found to be smaller in both medicated and unmedicated patients with schizophrenia, compared with healthy controls (Shi et al., 2016). Although the majority of studies of Asian patients have reported a reduction of ASR and its habituation in patients with schizophrenia (Table 1), these features are not consistently observed in Caucasian patients with schizophrenia (Braff et al., 2001a, 2001b;

Table 1
Summary of studies on acoustic startle response and its modulation in Asian patients with schizophrenia.

Study	SCZ	Age [years] (mean ± SD)	HP	Age [years] (mean ± SD)	PI (dB SPL)	LI (msec)	ITI (sec)	Main findings
Kunugi et al., 2007	20 (chronic) Male 12	42 ± 9	16 Male 9	41 ± 13	82, 86, 90	30, 60, 120	10–20 Average 15	ASR, PPI at 120 msec LI smaller in SCZ than in HP.
Takahashi et al., 2008	51 Male 29	38.1 ± 10.2	55 Male 28	40.4 ± 10.1	82, 86, 90	120	15–25 Average 20	HAB, PPI for all prepulse intensities smaller in SCZ than in HP.
Moriwaki et al., 2009	111 (chronic) Male 71	52.0 ± 1.46	110 Male 72	32.7 ± 0.674	82, 86, 90	120	15–25 Average 20	ASR, HAB, PPI for all prepulse intensities smaller in SCZ than in HP.
Wang et al., 2012	50 (chronic) Male only	data not shown	25 Male only	data not shown	85	30, 60, 120	11–19 Average 15	ASR, HAB, PPI at 120 msec LI smaller in SCZ taking typical antipsychotics compared to HP (25 treated with typical antipsychotics, 25 with clozapine).
Wang et al., 2013	31 Male 17	20.4 ± 4.5	30 Male 13	22.1 ± 3.5	85	30, 60, 120	11–19 Average 15	ASR, PPI at 60 msec LI smaller in SCZ than in HP (first-episode, medication-naïve).
Kishi et al., 2013	100 (chronic) Male 66	50.8 ± 15.5	107 Male 71	32.7 ± 7.16	82, 86, 90	120	15–25 Average 20	ASR, HAB, PPI for all PIs smaller in SCZ than in HP.
Matsuo et al., 2016	181 Male 83	37.6 ± 11.2	250 Male 125	36.7 ± 12.4	86, 90	60, 120	10–20 Average 15	ASR, HAB, PPI at 90 dB PI and 60, 120 msec LI smaller in SCZ than in HP.
Kishi et al., 2010	141(chronic) Male 91	49.8 ± 15.6			82, 86, 90	120	15–25 Average 20	PPI at 90 dB SPL PI was larger in SCZ taking aripiprazole or risperidone compared to those taking olanzapine.
Kishi et al., 2012	100 (chronic) Male 66	50.8 ± 15.5			82, 86, 90	120	15–25 Average 20	HAB was associated with level of attention in SCZ.

Background noise intensity 70 dB SPL, pulse duration 40 msec, and pulse intensity 115 dB SPL, prepulse duration 20 msec in all studies. ASR: acoustic startle response; HAB: habituation; HP: healthy participants; ITI: Inter-trial intervals; LI: lead interval from prepulse onset to pulse onset; PI: prepulse intensity; PPI: prepulse inhibition of ASR; SCZ: patients with schizophrenia; SPL: sound pressure level.

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Cadenhead et al., 2000; Geyer and Braff, 1982; Kumari et al., 2002). Thus, reduced PPI might be a global common psychophysiological feature of schizophrenia, while reduction in habituation or ASR in schizophrenia might differ between racial groups.

However, as is the case with studies from western countries, the relationships between startle measures and clinical variables have been inconsistent in Asian countries. Some studies (Kunugi et al., 2007; Takahashi et al., 2008; Wang et al., 2012) did not report any significant relationship between startle measures and clinical variables, while a negative correlation between PPI and cognitive symptoms has been reported in Asian men (Matsuo et al., 2016). Habituation of the ASR has also been demonstrated to be significantly related to cognitive functioning, such as the level of attention assessed by brief cognitive testing (Kishi et al., 2012).

A deficient PPI has also been observed in Japanese patients with schizotypal personality disorder (Takahashi et al., 2010), and to a lesser extent in normal Japanese participants scoring highly on psychometric measures of psychosis proneness (Takahashi et al., 2012), findings that are in line with earlier studies from Western countries (Cadenhead et al., 1993, 2000) (Swerdlow et al., 1995). The involvement of the cortico-striato-thalamic-pallido-pontine circuit in PPI of patients with schizophrenia and healthy controls in western countries (reviewed in Takahashi et al., 2011), was also found in healthy Asian women (Ota et al., 2013).

PPI is considered to be affected by several factors, including gender, smoking, and medication (in particular antipsychotic medication), and to involve several neurotransmitter pathways (Braff et al., 2001b; Geyer, 2006; Geyer et al., 2001; Swerdlow et al., 1994, 2008), including the dopaminergic, glutamatergic, serotonergic, and cholinergic pathways. Studies performed in western countries have frequently reported on the effects of medication status on the enhancement of PPI (Duncan et al., 2006), especially in relation to the atypical antipsychotics (Braff et al., 2001a; Duncan et al., 2003; Kumari et al., 2002; Perry et al., 2002; Swerdlow et al., 2006; Wynn et al., 2007). Such findings have also generally been observed in Asia (Kishi et al., 2010; Wang et al., 2012), although at least one study did not report such an effect (Xue et al., 2012).

In conclusion, studies from Asian countries suggest that reduced PPI is a promising global endophenotype of schizophrenia. Investigation of the mechanisms behind the development of reduced PPI across genotypes will contribute to a better understanding of the fundamental neural mechanisms underlying sensorimotor gating, and will certainly be most valuable in devising future approaches that aim to investigate the complex pathogenesis of psychiatric disorders.

3. Acoustic startle response and its modulation in children with ASD

ASD covers a set of heterogeneous neurodevelopmental conditions characterized by early-onset difficulties in social communication and unusually restricted repetitive behavior and interests (American Psychiatric Association, 2013). ASD severely impacts individuals throughout childhood and adulthood (American Psychiatric Association, 2013).

Sensory abnormalities are frequently present in individuals with ASD (Gomes et al., 2008; Marco et al., 2011), and have been considered a key feature of ASD since the pioneering reports of Kanner (1943). In particular, auditory over-responsiveness (AOR) is the most common sensory-perceptual abnormality in individuals with ASD (Gomes et al., 2008), and has been reported to interrupt behavioral adaptation (Lane et al., 2010).

Among the ASR indices, a basic index such as a greater ASR magnitude to weak stimuli may serve as a promising marker for translational research, especially in the context of auditory hyper-reactivity. Previous studies have typically used single high-intensity acoustic stimuli to evaluate the startle response and its modulation, and most have not reported any significant differences in startle magnitude between control children and children with ASD (Ornitz et al., 1993; Yuhas et al., 2011) or other developmental disorders, such as attention deficit hyperactivity disorder (Hawk et al., 2003) and Tourette's syndrome (Swerdlow et al., 2001). Recent studies on a single ethnicity sample of children from Japan (Takahashi et al., 2016, 2014) reported that, in comparison with children with typical development (TD), those with ASD exhibit a prolonged peak-ASR latency and a greater ASR magnitude in response to weak stimuli of around 65–85 dB. These indices were related to quantitative autistic traits in ASD children (Takahashi et al., 2016), and were fair to moderately stable across a one-year follow-up period (Takahashi et al., 2017). Thus, a prolonged peak startle latency and enhanced startle response to weak startle stimuli may serve as promising neurophysiological markers for ASD.

PPI of the ASR was found to not differ between ASD and TD children in Japanese samples (Takahashi et al., 2016), which is in line with studies on children with autism from western countries (Ornitz et al., 1993; Yuhas et al., 2011). However, adults diagnosed with ASD, such as autism (Perry et al., 2007) or Asperger's syndrome (McAlonan et al., 2002), have been reported to exhibit PPI impairments.

Modulation of the startle reflex is not consistent through childhood to adulthood. The neurophysiological mechanisms of PPI are considered to undergo development during early childhood, and do not mature until about 8 years of age in both male and female subjects (Ornitz et al., 1986, 1991). In adults, PPI is considered to be a stable index of individual sensorimotor gating (Cadenhead et al., 1999) over a long time interval of one year (Light et al., 2012), and even over a 15-year period (Swerdlow et al., 2017). A recent study of Japanese children reported that ASR indices, including PPI, were moderately stable indices in TD and ASD children of 8–16 years of age (Takahashi et al., 2017) over an interval of one year. Studies on early psychosis (Cadenhead, 2011; Quednow et al., 2008a; Ziermans et al., 2011) suggest that PPI disruption is present before the onset of psychosis. Although PPI did not differ significantly between children with ASD compared to those with TD, PPI was related to the emotional/behavioral problems of children (age 8–16 years) with ASD and TD (Takahashi et al., 2016). These studies suggest that PPI might be a promising neurophysiological index related to comorbid psychiatric conditions for patients over 8 years of age. Future studies investigating the mechanisms of PPI maturation in early development of ASD may contribute to further understanding of preventing future comorbid psychiatric disorders in children with ASD.

4. Conclusion

Recent studies from Asia support the idea that the ASR and its modulation, including PPI, is a well-established global neurophysiological index for translational research in psychiatric and neurodevelopmental disorders. Studies of PPI have successfully contributed to a better understanding of the fundamental neural mechanisms underlying sensorimotor gating, and will be valuable for devising new approaches for investigating the complex pathogenesis of schizophrenia across racial groups. In addition, studies of PPI in children with ASD suggest that future studies investigating the development of sensorimotor gating in early development may also contribute to prevention of psychiatric disorders.

Abbreviations

ASD	autism spectrum disorder
ASR	acoustic startle response
PPI	prepulse inhibition
TD	typical development

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Contributors

Author HT designed the study and wrote the protocol. Author HT managed the literature searches and analyses. Authors HT and YK wrote the manuscript. Author HT wrote the first draft of the manuscript. All authors have contributed to and approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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