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Meta-analysis of sensorimotor gating in patients with autism spectrum disorders

Chia-Hsiung Cheng[a,b,c,d,*], Pei-Ying S. Chan[a,c,d], Shih-Chieh Hsu[d,e], Chia-Yih Liu[d,e]

[a] Department of Occupational Therapy and Graduate Institute of Behavioral Sciences, Chang Gung University, Taoyuan, Taiwan
[b] Laboratory of Brain Imaging and Neural Dynamics (BIND Lab), Chang Gung University, Taoyuan, Taiwan
[c] Healthy Aging Research Center, Chang Gung University, Taoyuan, Taiwan
[d] Department of Psychiatry, Chang Gung Memorial Hospital, Linkou, Taiwan
[e] School of Medicine, Chang Gung University, Taoyuan, Taiwan

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ABSTRACT

Prepulse inhibition (PPI) of startle response is a well-established neurophysiological marker of sensorimotor gating ability in psychiatric patients including those with autism spectrum disorders (ASD). PPI has been utilized as an indicator of the central inhibitory function and is potentially linked to the clinical features of this disease. However, it remains inconclusive whether ASD patients exhibit PPI deficits compared with healthy controls. The present meta-analysis aimed to explore the pooled effect sizes of PPI in ASD patients. We searched major electronic databases from 1990 to January 2017. Seven studies, consisting of 21 individual investigations with 135 healthy controls and 99 ASD patients, were obtained. The effect size, calculated as Hedges's g and 95% confidence interval, were estimated. Overall, we found ASD patients exhibited an impaired PPI compared with healthy controls ($p = 0.008$). Specifically, significant PPI deficits were observed among ASD children/adolescents, compared with their healthy counterparts ($p = 0.019$). However, differences in PPI responses were not observed among adults. Conclusively, our results reconciled the previous studies and showed that ASD children/adolescents, but not adults, exhibit reduced sensorimotor gating function compared to healthy controls. We also suggest that the parameters of PPI are particularly important and the results should be interpreted with cautions.

1. Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders with problems in social interaction, communication, and behaviors (Wing, 1996). Recent studies have also revealed that ASD patients have deficits in attention and perception in addition to executive dysfunctions (Guillon et al., 2016; Karaminis et al., 2016). It was estimated that about 90% of ASD patients demonstrated sensory abnormalities (Kern et al., 2006; Leekam et al., 2007), particularly in the form of auditory hypersensitivity (Baron-Cohen et al., 2009; Hitoglou et al., 2010).

Dysfunction in sensory processing may lead to sensorimotor gating deficits. Sensorimotor gating is an automatic inhibitory mechanism to regulate sensory inputs by filtering out irrelevant sensory information in the central nervous system. This protective process allows the human brain to gate out distracting stimuli and to appropriately react to relevant stimuli (Braff et al., 1978, 1999). Prepulse inhibition (PPI) of acoustic startle responses has been considered as an optimal neurophysiological indicator of sensorimotor gating, and has been tested in many psychiatric diseases, such as schizophrenia (Braff et al., 2001a, 2001b), obsessive-compulsive disorder (Hoenig et al., 2005; Ahmari et al., 2012), posttraumatic stress disorder (Holstein et al., 2010), and ASD (Takahashi et al., 2011). PPI is measured by a paired-click paradigm where a weak acoustic prepulse (PP) attenuates the startle reflex to a loud pulse (P) sound. In human studies, the electromyographic (EMG) responses to the orbicularis oculi muscle activities are recorded and used for PPI calculation. Quantitatively, PPI is generally expressed as [1 – (PP/P)*100%]. A larger PPI% value indicates a better sensorimotor gating function.

While impairments in PPI have been well-documented in schizophrenia (Braff et al., 2001a, 2001b), the results were controversial in patients with ASD. Ornitz and colleagues performed the first PPI study in ASD and found no significant sensorimotor gating deficit in autistic children and adolescents (Ornitz et al., 1993). Some studies on autistic children or adolescents also did not show PPI decline in this specific population (Yuhas et al., 2011; Oranje et al., 2013; Kohl et al., 2014; Takahashi et al., 2016). However, others have reported that adults with Asperger's syndrome (McAlonan et al., 2002) or high functioning autism (Perry et al., 2007) exhibited reduced PPI in certain testing

* Correspondence to: Department of Occupational Therapy and Graduate Institute of Behavioral Sciences, Chang Gung University, No. 259, Wenhua 1st Rd., Taoyuan City 333, Taiwan.
E-mail addresses: ch.cheng@mail.cgu.edu.tw, chiahsiung.cheng@gmail.com (C.-H. Cheng).

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conditions. Moreover, Madsen and colleagues found an enhancement of PPI in children with ASD compared with healthy children (Madsen et al., 2014). The discrepancies in findings among the previous studies may be related to several factors. Firstly, the experimental parameters were vastly different across studies. Levels of the acoustic intensity of prepulse and startling (i.e., pulse) stimuli, the stimulus onset asynchrony (SOA)/interstimulus interval (ISI) between prepulse and startling stimuli, or the duration of the clicks were highly varied. Secondly, subject age was not consistent across studies, where some recruited children and adolescents and others collected data from adults with ASD. Thirdly, the smaller number of participants in some studies may have led to a lack of statistical power.

Meta-analysis is considered as an objective tool to summarize the results that show heterogeneities in previous studies. To the best of our knowledge, there has been no statistical review on PPI in patients with ASD. Therefore, the major goal of the present study was to systematically review the available data and explore whether patients with ASD showed deficient sensorimotor gating, as indexed by PPI, compared with healthy subjects. In addition, we aimed to investigate the effects of age groups (children/adolescents versus adults) on PPI in ASD patients.

2. Methods

2.1. Literature search and study selection

A literature search was carried out in PubMed and Medline 1990–2017 January), using combinations of the keywords “autism”, “Asperger's syndrome”, “prepulse inhibition”, and/or “sensorimotor gating”. Furthermore, additional articles were obtained from the references listed in the studies identified in PubMed and Medline. Only peer-reviewed published articles were considered in the present meta-analysis.

The first two authors (Cheng and Chan), independently reviewed and identified studies that met the following inclusion criteria: 1) must be human studies, 2) must include at least one ASD group and one comparison group, 3) group differences in PPI% must be reported either in terms of means (M) and standard deviations (SD), or as *t*-test or F test, and 4) the content must be written in English. The necessary data of each study regarding the subtypes of ASD, case number, age, intelligence quotient, auditory hypersensitivity, stimulus characteristics, and M and SD of PPI% were extracted by Cheng and then checked by Chan. In the case of disagreements with study criteria, consensus was reached through discussion. If more than one condition was found in the study (e.g., different ISIs/SOAs or different intensities of prepulse stimuli), each condition was considered as an individual investigation. This method has been validated in previous studies (Cheng et al., 2013, 2016a, 2016b).

2.2. Data synthesis

All calculations were performed using the Comprehensive Meta Analysis 3.0 software (Biostat, Inc., Englewood, New Jersey). Effect sizes of the random-effect model were calculated as Hedges's g and 95% confidence interval (CI), on the basis of either 1) group mean differences between the ASD and control groups, divided by pooled SD, 2) Cohen's d and sample sizes, or 3) *t*-test or F test. The effect sizes for the moderator variable (i.e., age group) were also investigated. In the present meta-analysis, we defined those younger than 18 years as children/adolescents, and those 18 years or older as adults. To overcome the influences of sample size on the effect sizes, an inverse variance weighting factor was applied to give more weights on studies with larger sample sizes. Effect sizes of Hedges's g between 0.2 and 0.5 were categorized as small, those between 0.5 and 0.8 were categorized as medium, and those above 0.8 were categorized as large (Cohen, 1992). The statistical heterogeneity was quantified using Q-statistics and I^2 index.

A funnel plot was created to assess publication bias. A more symmetrical shape is considered less biased between smaller-size and larger-size studies. Furthermore, Begg-Mazumdar Kendall's tau (Begg and Mazumdar, 1994) and Egger's regression intercept tests (Egger et al., 1997) were used to determine whether there was a potential presence of publication bias. A *p*-value less than 0.05 was set as the significant threshold.

3. Results

3.1. Study characteristics

A total of 84 articles were identified in the initial search. After screening, 9 eligible studies were obtained. Based on the full-text review, one study did not provide sufficient statistical data (Ornitz et al., 1993), and another study did not recruit healthy controls for comparisons (Ebstein et al., 2009). Therefore only 7 studies were included in the meta-analysis (McAlonan et al., 2002; Perry et al., 2007; Yuhas et al., 2011; Oranje et al., 2013; Kohl et al., 2014; Madsen et al., 2014; Takahashi et al., 2016). Six of the 7 studies included more than one condition, and thus a total of 21 individual investigations were used in the final analysis. Fig. 1 displays the flowchart for the literature search process.

Table 1 summarizes the characteristics of the analyzed studies, including sample size, age, diagnosis, and experimental parameters. The number of the participants ranged from 11 to 34 for the control groups (135 total) and from 11 to 18 for the ASD groups (99 total). The auditory hypersensitivity in ASD was identified according to the amplitudes of acoustic startle responses compared with healthy controls. Among these studies, 4 assessed PPI in ASD children or adolescents (Yuhas et al., 2011; Oranje et al., 2013; Madsen et al., 2014; Takahashi et al., 2016), and 3 assessed PPI in ASD adults (McAlonan et al., 2002; Perry et al., 2007; Kohl et al., 2014).

3.2. Effect sizes

Fig. 2 depicts the pooled effect sizes and 95% CIs of PPI% for each investigation. Results from the meta-analysis revealed that ASD patients showed reduced PPI% ($g = 0.230$, 95% CI: 0.059–0.402, $p = 0.008$) compared with the control group. We did not find a robust heterogeneity across the studies ($Q = 27.42$, $I^2 = 27.05\%$, $p = 0.124$).

Since previous studies suggested differential sensorimotor gating abilities between ASD adults and children/adolescents, we further investigated the effect of age groups on PPI ability. As shown in Fig. 3(A), the meta-analytic results demonstrated that ASD children or adolescents had a declined PPI%, relative to the healthy participants ($g = 0.255$, 95% CI: 0.041–0.468, $p = 0.019$). However, the effect size was not statistically significant in the comparisons between ASD adults and healthy controls, as shown in Fig. 3(B) ($g = 0.195$, 95% CI: -0.098 to 0.489, $p = 0.192$).

3.3. Publication bias

The funnel plot of PPI% displays a relatively symmetrical shape, indicating no publication bias between smaller-size and larger-size studies (Fig. 4). The Begg and Mazumdar rank correlation (Kendall's tau $= 0.02$, $p = 0.88$), and Egger's regression intercept (intercept $= -0.13$, $p = 0.94$) also confirmed that the observed results did not suffer from publication bias.

4. Discussion

The current meta-analysis is the first quantitative review on sensorimotor gating ability in patients with ASD. Our results identified 7 studies and found that sensorimotor gating, as indexed by PPI%, was