



Multisensory temporal binding window in autism spectrum disorders and schizophrenia spectrum disorders: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:

Temporal binding window
Multisensory
Unisensory
Autism spectrum disorders
Schizophrenia spectrum disorders
Meta-analysis

ABSTRACT

Multisensory temporal integration could be compromised in both autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) and may play an important role in perceptual and cognitive impairment in these two disorders. This review aimed to quantitatively compare the sensory temporal acuity between healthy controls and the two clinical groups (ASD and SSD). Impairment of sensory temporal integration was robust and comparable in both patients with SSD (Hedges' $g = 0.91$, 95%CI[0.62–1.19]; $Z = 6.21$, $p < .001$) and ASD (Hedges' $g = 0.85$, (95%CI[0.54–1.15]; $Z = 5.39$, $p < .001$). By further separating studies into unisensory and multisensory (bimodal: audiovisual) ones, subgroup analysis indicated heterogeneous and unstable effects for unisensory temporal binding in the ASD group, but a more consistent and severe impairment in multisensory temporal integration represented by an enlarged temporal binding window in both clinical groups. Such multisensory dysfunction is associated with symptoms like hallucinations and impaired social communications. Future studies focusing on improving multisensory temporal functions may have important implications for the amelioration of schizophrenia and autistic symptoms.

1. Introduction

After the establishment of autism as a separate category from early-onset schizophrenia in DSM-III (American Psychiatric Association, 1987), autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) have been considered distinct disease entities with different aetiologies, clinical manifestations and diagnostic classification. However, substantial findings have shown that these two “distinct” clinical entities may in fact be closely related and may even lie on the same continuum of neurodevelopmental disorders (King and Lord, 2011). The two disorders share significant overlap in genetics (Carroll and Owen, 2009), connectivity deficits (Friston et al., 2016; Just et al., 2004) and impaired social cognition (Pinkham et al., 2008). There is also a high rate of co-morbidity between schizophrenia and autism/pervasive developmental disorders in both children (Rapoport et al., 2009) and adults (Chisholm et al., 2015). On the other hand, results from comparative studies have suggested that different underlying

mechanisms may account for these apparent similarities (Crespi and Badcock, 2008; Crespi et al., 2010; Russell-Smith et al., 2010). Examining this overlap using a trans-diagnostic approach may help to advance our understanding of these two disorders.

One of the hallmark features of both disorders is sensory and multisensory dysfunctions (Baum et al., 2015; Tseng et al., 2015). Sensory abnormalities are prominently prevalent in ASD (Baranek et al., 2006) and are now included as a core symptom of this disorder in the DSM-5 (American Psychiatric Association, 2013). Considering early sensory stages and local processing, a subgroup of autistic children has been shown to possess improved sensory acuity (e.g., recognizing perfect pitch, superior ability to discriminate visual appearance with minor changes) (Happé and Frith, 2006; Mottron et al., 2006; Mottron et al., 2009). However, when it comes to high-level global function and multisensory interactions, robust and consistent impairment has been demonstrated in ASD (see reviews, Baum et al., 2015; Wallace and Stevenson, 2014), with neuroimaging evidence showing failure to

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activate large-scale cortical networks (Damarla et al., 2010) and reduced long range connectivity (Damarla et al., 2010; Glazebrook and Wallace, 2015). Thus, it is important to extend beyond unisensory function to further investigate multisensory integration in ASD. As for SSD, basic unisensory deficits including impaired auditory gating and fragmented visual perception may underlie abnormal perceptual experience (e.g., hallucinations) and difficulties in interpersonal and social interactions (Javitt and Freedman, 2015). Beyond unisensory function, a recent review has demonstrated the presence of deficits in integrating cross-modal information, especially audiovisual linguistic stimuli in patients with schizophrenia (Tseng et al., 2015). Neuroimaging studies have reported that multisensory deficits in schizophrenia are associated with alterations in brain networks responsible for sensory and language functioning, including the superior and inferior frontal cortices, and the superior and middle temporal cortices (Sass et al., 2014; Straube et al., 2014; Szykic et al., 2013). Other subcortical regions like the thalamus, which is consistently found to be dysfunctional in schizophrenia (Cobia et al., 2017; Giraldo-Chica and Woodward, 2016), may also affect multisensory performance in this clinical group. Multisensory processing may therefore serve as a “gateway” to investigate the underlying pathology of ASD and SSD.

In this study, we specifically focused on the temporal factor of multisensory integration as accumulating evidence supports its relevance in neurodevelopmental disorders (Wallace and Stevenson, 2014) since Brock et al. (2002) first put forward the temporal binding hypothesis to explain sensory abnormalities in ASD. “Temporal Binding Window” (TBW), an epoch of time within which paired stimuli are highly likely to be bound, is a concept commonly used to reflect multisensory temporal function or acuity. Two of the most common paradigms to measure the width of TBW are the Simultaneity Judgement (SJ) and the Temporal Order Judgement (TOJ) task. In these tasks, participants are asked to judge the relative timing of an auditory and visual stimulus with different stimulus onset asynchronies (SOA) (i.e., “Were the auditory and visual stimuli presented at the same time?” for SJ and “Which stimulus came first?” for TOJ). Rates of perceived simultaneity or accuracy for judging temporal order across different SOAs are used to calculate the width of the TBW. Typically, the time interval between 75% threshold of the audio-first presentations and visual-first presentations is defined as the individual’s TBW (Stevenson et al., 2017a). Within this “window”, participants have a high probability of reporting simultaneity and find it hard to discriminate the temporal order of the paired sensory stimuli. An extended TBW reflects imprecise temporal processing of sensory stimuli. Combining sensory information which could be distinguished by individuals with a narrower TBW may result in sensory overload, ambiguous perceptual identity and perception of an improperly filtered confusing world (Sartorato et al., 2017). It may also undermine speech comprehension (Stevenson et al., 2012), contribute to reading difficulties (Hairston et al., 2005), and result in hallucinations (Stevenson et al., 2017a) and a disturbed sense of “self” (Postmes et al., 2014).

Developmentally, multisensory TBW tends to be longer in late adolescence, progressively shortens in adulthood (Hillock-Dunn and Wallace, 2012), and gradually lengthens again with ageing (Diederich et al., 2008; Setti et al., 2011). In clinical populations, previous findings have demonstrated multisensory temporal dysfunction indexed by a prolonged sensory TBW in both ASD and SSD (Wallace and Stevenson, 2014). However, little is known about the differences and similarities of the underlying mechanisms underlying the prolonged TBW in these two clinical groups. The aim of this study was to quantitatively review the literature on sensory temporal integration impairment in ASD and SSD. In addition, we examined the unsolved issues of multisensory impairments in these two clinical groups and discussed the future directions for multisensory integration.

2. Methods

2.1. Literature search

Four authors (HYZ, PB, XLC, MW) independently conducted literature search in PubMed, PsychoInfo, Web of Knowledge and Academic Search Complete for peer-reviewed, original studies published up to May 12, 2017. We included papers in all languages. The following terms were used: (“temporal binding window” OR “temporal binding” OR “binding window” OR “temporal processing” OR “temporal integration” OR “binding problem”) AND (schizo* OR autis*). In addition, the reference lists of all included studies and three relevant systematic reviews (Baum et al., 2015; Tseng et al., 2015; Wallace and Stevenson, 2014) were also manually searched for further relevant studies. Studies were included if they met the following criteria: 1) used an appropriate paradigm for (multi-)sensory temporal processing. Two of the most common paradigms are the SJ Task and the TOJ Task mentioned earlier. Other possible paradigms include the Sound-induced-Flash Illusion Task and the McGurk task with different audiovisual SOAs. In the Sound-induced Flash Illusion Task, one flash is accompanied by two sound stimuli to induce double flash illusion. The first sound coincides with the onset of the flash, while the second sound is presented with a delay after the first flash-sound pair. The intensity of audiovisual integration is indicated by the amount of perceived illusions, which depends on the influence of auditory stimuli on vision. As defined by Foss-Feig et al. (2010), the multisensory TBW is the span of illusory SOAs where the mean percentage of reported double flashes is significantly greater than the mean percentage of reported double flashes in the control condition (i.e., one flash one sound). In the McGurk task, the percentage of perceived “da” for mismatched audiovisual stimuli (visual “ga” and auditory “ba”) is the proxy for the intensity of multisensory integration. The mean rates of McGurk fusion across different SOAs are normalized to an individual’s maximum fusion rate, and then used to calculate the width of the TBW within which fusion is reported for at least 75% of the trials (Woynarowski et al., 2013). It is important to note that one study (Grimsen et al., 2013) we included in our meta-analysis used a seemingly irrelevant paradigm. However, a further examination suggested that the temporal figure-and-ground segmentation task used in this study measured an individual’s visual asynchrony detection ability (Grimsen et al., 2013). In other words, this paradigm was a variant of the SJ task and thus was also included in our meta-analysis. 2) included a clinical sample (either schizophrenia or autism spectrum disorders) and a healthy control group; and 3) provided sufficient data for calculating effect size. Specifically for Criterion 3, we extracted the reported means, standard deviations and sample sizes for patient and control groups. If the means and standard deviations were not reported, effect sizes were calculated based on the *t* or *F* values and the sample sizes. If one study met the first two criteria but failed to fulfill the third, they were excluded from the meta-analysis but retained in the systematic review (see in Table 1). We excluded the studies if they met any of the following exclusion criteria: 1) the study was a review, meta-analysis, comment or a dissertation paper; 2) the study did not have an appropriate paradigm which was specific to (multi-)sensory temporal binding; and 3) the study only involved non-clinical samples or clinical groups (e.g. ADHD) other than schizophrenia and ASD.

2.2. Data extraction

First, all the included studies were separated into four subgroups randomly. Then, demographic and clinical characteristics (sample size, age, gender, clinical symptoms, medication, illness duration and comorbidities), study design (paradigm, sensory modality and stimulus type), mean differences in the widths of TBWs or raw data were extracted independently by four authors (HYZ, PB, XLC, MW) for each subgroup. Finally, the first author (HYZ) thoroughly went through all

Table 1
Summary of (multi-)sensory temporal binding windows in schizophrenia spectrum disorders (SSD) and autism spectrum disorders (ASD).

Autism	Authors		Method and Task paradigm			Sample size	Main findings
	Paradigm	Sensory modal	Stimuli type				
	Stevenson et al. (2014)	Simultaneity Judgement	auditory, visual and audiovisual	nonspeech (flashbeep, tool), speech	32 ASD, 32 TD (children & adolescents)	(1) Extended TBW only restricted to audiovisual speech stimuli; (2) the widths of TBW across stimuli types were correlated with the strength of the McGurk effect in ASD group.	
	Noel et al. (2017)	Simultaneity Judgement	audiovisual	nonspeech (flashbeep, tool), speech	26 ASD, 26 TD (children & adolescents)	Extended TBW only restricted to audiovisual speech stimuli in ASD.	
	Woynarowski et al. (2013)	Identification task of McGurk stimuli with different audiovisual SOAs	auditory, visual and audiovisual	speech	18 ASD, 18 TD (children & adolescents)	(1) Extended TBW in ASD group indicated by McGurk perception of different audio-visual SOAs; (2) reduced multisensory integration was significantly associated with communication deficit; increased McGurk fusion was correlated with auditory processing abnormalities and inattention in ASD.	
	de Boer-Schellekens et al. (2013a)	Temporal Order Judgement	audiovisual	nonspeech (flashbeep), speech	16 ASD, 16 TD (young adults)	Individuals with ASD were less sensitive perceiving small audiovisual timing differences than controls, but they were not specifically impaired with audiovisual speech stimuli.	
	de Boer-Schellekens et al. (2013b)	Visual Temporal Order Judgement task; Multisensory Temporal Order Judgement task with irrelevant auditory stimuli added to visual task	visual; audiovisual	nonspeech (flashbeep)	35 ASD, 40 TD (young adults)	(1) Impaired visual temporal acuity in ASD BUT (2) intact audiovisual integration (Irrelevant sound improves visual temporal order judgement performance in a similar way between ASD and TD).	
	Wada et al. (2015)	Tactile Temporal Order Judgement task with arms-uncrossed and arms-crossed	tactile	nonspeech	10 ASD, 10 TD (children & adolescents)	(1) Impaired tactile temporal acuity in ASD (2) smaller cross-hands illusory reversal due to over-reliance on proprioception.	
	Falter et al. (2012)	Simultaneity Judgement	visual	nonspeech	16 ASD, 16 TD (adults)	Improved visual temporal acuity in ASD.	
	Kwakye et al. (2011)	Visual and Auditory Temporal Order Judgement tasks; Multisensory Temporal Order Judgement task with irrelevant auditory stimuli added to visual task	auditory, visual and audiovisual	nonspeech (flashbeep)	35 ASD, 27 TD (children & adolescents)	(1) Extended TBW (approximately doubled widths of TBW) in ASD indicated by more improvement in accuracy of visual temporal order judgement task when an irrelevant beep was added in larger SOAs; (2) impaired auditory temporal processing in ASD.	
	Foss-Feig et al. (2010)	Sound-induced Flash Illusion	audiovisual	nonspeech (flashbeep)	21 ASD, 17 TD (children & adolescents)	Extended TBW in ASD, roughly twice the size as TDs	
	Greenfield et al. (2015)	Modified Rubber Hand Illusion task (with a proprioceptively aligned arm and a displaced arm)	visual-tactile	nonspeech	29 ASD, 29 chronological-age-matched HC, 29 verbal-mental-age-matched HC (children & adolescents)	(1) Extended visual-tactile TBW and (2) a greater reliance on proprioception in ASD.	
Schizophrenia	Stevenson et al. (2017a)	Simultaneity Judgement	auditory, visual and audiovisual	nonspeech (flashbeep), speech	16 chronic SCH, 16 HC	(1) General impaired temporal acuity across sensory modalities in SCH, (2) extended audiovisual TBW that goes beyond what can be explained by unisensory dysfunction ; (3) the widths of the TBW were significantly correlated with hallucination severity, in that the wider the TBW, the less severe their hallucinations were.	
	Foucher et al. (2007)	Simultaneity Judgement	auditory, visual and audiovisual	nonspeech (flashbeep)	30 chronic SCH, 33 HC	(1) General impaired temporal acuity across sensory modalities in SCH; (2) low temporal resolution was correlated with the disorganization symptoms but not with the dosage of chlorpromazine equivalent.	
	de Boer-Schellekens et al. (2014)	Visual Temporal Order Judgement task; Multisensory Temporal Order Judgement task with irrelevant auditory stimuli added to visual task	visual, audiovisual	nonspeech	16 chronic SCH, 16 HC	(1) Impaired visual temporal acuity BUT (2) intact audiovisual integration (irrelevant sound improves visual temporal order judgement performance in a similar way between SCH and HC).	
	Giersch et al. (2009)	Simultaneity Judgement	visual	nonspeech	19 chronic SCH, 19 HC	Impaired visual temporal acuity /extended visual simultaneity threshold in SCH.	
	Schmidt et al. (2011)	Simultaneity Judgement	visual	nonspeech	20 SCH (9 chronic, 11 first-episode), 11 HC	Extended visual simultaneity threshold in SCH.	

(continued on next page)

Table 1 (continued)

Authors	Method and Task paradigm			Sample size	Main findings
	Paradigm	Sensory modal	Stimuli type		
Capa et al. (2014)	Temporal Order Judgement	visual	nonspeech	20 chronic SCH, 20 HC	(1) Impaired visual temporal order judgement , especially in the case of long asynchronies in SCH; (2) SCH patients can detect asynchrony but fail to order events one after another, which may lead to a disorganization in time. (1) Extended threshold of asynchrony detection (about 20% increase) in SCH. (2) For asynchronies below threshold, SCH's responses were biased to the side of the first stimuli while HC's responses were biased to the side of the second stimuli (i.e., inverse Simon effect in two groups), which indicated impaired perception of succession and predictive coding in SCH.
Lalanne et al. (2012)	Simultaneity Judgement	visual	nonspeech	18 chronic SCH, 18 HC	Asynchrony detection was intact in SCH and no prolonged temporal integration was found. Impaired visual temporal acuity in SCH.
Grimsen et al. (2013)	Temporal Figure-Ground- Segmentation	visual	nonspeech	18 chronic SCH, 15 HC	(1) Extended audiovisual TBW in SCH; (2) no correlation with clinical symptoms was found.
^a Tenckhoff et al. (2002)	Temporal Order Judgement	visual	nonspeech	27SCH (18 chronic,9 first-episode), 18HC	(1) No difference of the McGurk illusory perception between SCH and HC; (2) the illusory reports of patients in the implicit identification task were more sensitive to audiovisual speech asynchronies than those of controls; (3) extended audiovisual TBW indicated by explicit SJ task in SCH; (4) separated results of explicit temporal tolerance observed in Simultaneity Judgement task and implicit sensory binding indicated by McGurk illusion in SCH.
^a Haß et al. (2017)	Sound-induced Flash Illusion	audiovisual	nonspeech	15 chronic SCH, 15 HC	
^a Martin et al. (2013)	McGurk task: Identification (implicit) & Simultaneity Judgement (explicit)	audiovisual	speech	26 SCH, 26 HC (Only subgroups for comparison)	

SCH, schizophrenia patients; HC, healthy controls; ASD, participants with autism spectrum disorders; TD, typically developing participants. TBW, temporal binding window.

^a Studies **NOT included** in the meta-analysis due to insufficient data for effect size calculation.

the included papers to extract data again. No conflict of the extracted data was found between the four authors.

2.3. Quality assessment of individual studies

To examine potential risks of bias on individual-study level, two authors (HYZ and XLC) independently evaluated the studies included in this meta-analysis. Our quality assessment followed an eight-item scale where one point was given to each of the following criteria:

- The study used a recognized diagnostic system to ascertain clinical diagnoses.
- Healthy controls had no personal or family history of any psychiatric disorders.
- The sample size was large enough for statistical testing (at least 20 cases for each group).
- Patients and controls were demographically matched (i.e., age and gender ratio).
- The study used controls that were matched for education level for SSD, and matched for IQ for ASD.
- The study used paradigms that were suitable for *directly* measuring TBW, including the SJ task, the TOJ task, the Sound-Induced Flash Illusion task or the McGurk task with different SOAs as mentioned in section 1 and 2.1.
- The study directly compared the width of TBW (using Simultaneity Thresholds or Just Noticeable Difference) between patients and controls. (If the analyses only used accuracy rates across SOAs to indicate and compare temporal acuity, no point was given.)
- The study had sufficient number of trials to reliably assess temporal acuity, defined as at least five different SOAs and at least 20 trials for each SOA.

The first five items were adapted from the Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis (Wells et al., 2014). Items g) to h) were added to evaluate the validity and reliability of the experimental paradigm.

2.4. Data analysis

All analyses were conducted in the computer program Comprehensive Meta-Analysis (version 2.2.064). Hedges' g , a variation of Cohen's d that accounts for sample size bias (Hedges and Olkin, 1985), was used to calculate effect sizes for the difference in (multi-)sensory temporal function between clinical groups and healthy controls. Effect size estimates were pooled across studies within the same clinical group to obtain an overall effect size for schizophrenia and ASD respectively. The random-effects model was reported given the heterogeneity of these studies (Hedges and Vevea, 1998). After computing the summary effect and its standard error, we performed a Z test of the null hypothesis.

To further compare the severity of sensory temporal integration problem between schizophrenia and ASD, we used a simple Z-test to examine whether the difference between the two effects was significant. The formula of the test statistic is $Z_{diff} = (g_{SCH} - g_{ASD}) / \sqrt{(V_{SCH} + V_{ASD})}$, where g_{SCH} and g_{ASD} are the estimated mean effects underlying the schizophrenia and the ASD groups, and V_{SCH} and V_{ASD} are their variances (Borenstein et al., 2009).

Publication bias is a major concern in meta-analysis. We conducted the classic fail-safe N analysis, which indicates the number of unpublished studies needed to make the effect size estimate non-significant. If the number was greater than $5K + 10$ (where K is the number of studies included in the meta-analysis), it was interpreted to be a statistically robust effect size (Rosenthal and Rubin, 1988). We also conducted Begg & Mazumdar's rank correlation test to quantify the bias captured by the funnel plot (Begg and Mazumdar, 1994). The third method we used to evaluate publication bias was the Duval and

Tweedie's trim and fill procedure, which demonstrates how the effect size shifts after accounting for publication bias (Duval and Tweedie, 2000).

Heterogeneity was tested using the χ^2 and I^2 statistics, with a chi-square test $p < .05$ or $I^2 > 50\%$ indicating considerable heterogeneity (Higgins et al., 2003). The estimated variance of the true effect sizes denoted by T^2 was also reported. For further investigation of heterogeneity, we split the data file into subgroups investigating the same type of sensory modality (e.g. unisensory (visual or tactile) vs. multi-sensory (audiovisual)). We also conducted meta-regression analyses using the random-effects model (method of moments) to examine the relationship between effect sizes and other variables including age, gender ratio and publication year (Borenstein et al., 2009). The meta-regression analyses were conducted within each clinical group and also after combining all studies for age and gender, but were only conducted with all studies for publication year. For medication, we only conducted meta-regression within the SSD group ($n = 7$) rather than the ASD subgroup due to the limited number of papers providing such information ($n = 2$). The significance of the correlation between effect size and study-level variables was indicated by Z-values and its corresponding p value.

3. Results

3.1. Study characteristics

Fig. 1 illustrates the process of study selection. We identified 11 relevant studies for SSD and 10 studies for ASD. Description of the characteristics of all the 21 studies are summarized in Table 1. Seven studies did not provide sufficient data for effect size calculation, leaving 14 studies for the meta-analysis. Of the seven studies excluded, three could only provide an approximate width of the TBW at group-level rather than individual-level (Foss-Feig et al., 2010; Haß et al., 2017; Kwakye et al., 2011). Martin et al. (2013)'s study, which utilized the McGurk Task only analyzed the performance of a small subgroup of patients who reported McGurk fusion/combination and did not provide exact data for TBW comparison due to large variability across patients. Greenfield et al. (2015)'s visual-tactile study in ASD patients only used "frequency" data for its chi-square analysis and was thus excluded. A paper in German divided schizophrenia patients into two groups according to the medical condition and only compared the visual temporal acuity among the three groups (Tenckhoff et al., 2002). Finally, Falter et al. (2012) reported medians (quartile deviations) rather than means and standard deviations of the simultaneity thresholds in ASD adults and controls due to non-normality of their data.

The included studies had an average quality score of 6.07 (range = 4–7, median = 6). All studies used recognized diagnostic system, and most had clinical and control groups well-matched for demographic variables. Except Grimsen et al. (2013)'s study which used a variant of SJ task and Capa et al. (2014)'s study, which did not directly compare the width of TBW, other studies all used paradigms suitable for directly measuring and comparing TBW. However, only five studies had a relatively large sample ($n > = 20$ for each group). Although all studies had more than five different SOAs, only eight used at least 20 trials for each SOA to reliably assess the TBW. No study was excluded due to the poor reporting quality. More details about the quality evaluation can be found in Supplemental Table 1.

Eight studies included data for 157 schizophrenia patients and 148 healthy controls. Of these, six involved unisensory temporal processing (exclusively in the visual modality) and the remaining two focused on audiovisual temporal binding. Six studies investigated temporal binding function in ASD, which included a total of 137 autistic children and adults and 142 healthy controls. Of these, four involved audiovisual temporal binding window, one focused on visual temporal acuity and one investigated tactile temporal processing. Other study information including age, gender, and medication dosage of these 14 included

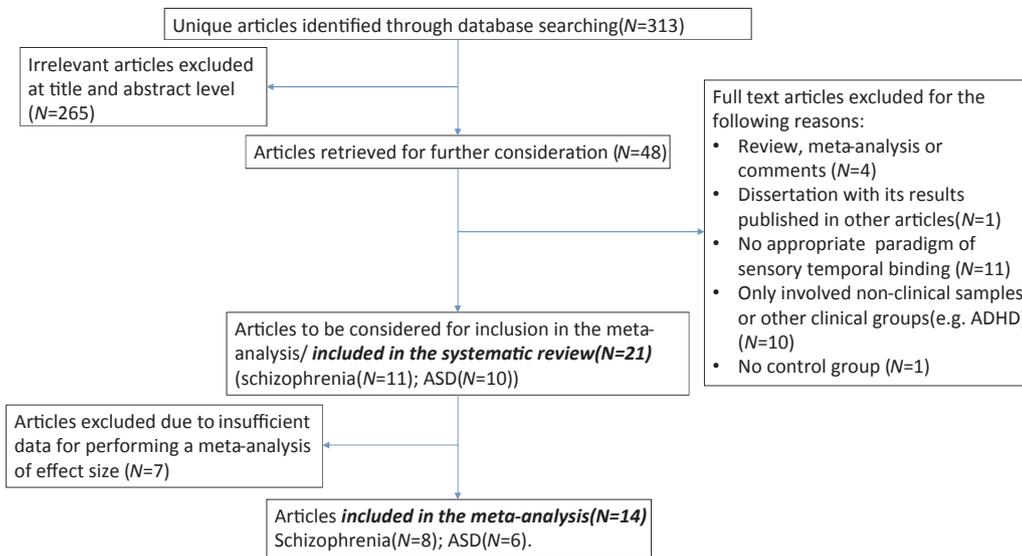


Fig. 1. Flow diagram of study selection process.

Table 2
Meta-analysis and subgroup analysis of impaired sensory temporal integration in autism and schizophrenia.

Author	Sensory modal	Sample size	Mean age of clinical samples (SD) (years)	Gender (% Male)	Medication Mean daily dosage (Eq CPZ) (mg)	Hedges' g (95%CI)
Autism (N of studies = 6): Hedges' g = 0.846, 95%CI [0.539–1.154]; Z = 5.393, p < .001; I² = 33.91%						
Stevenson et al.(2014)	audiovisual	32ASD, 32TD	12.3(2.3)	59.38%	/	0.862 (0.355–1.368) ^{***}
Noel et al.(2017)	audiovisual	26ASD, 26TD	11.6(3.8)	46.15%	/	0.596 (0.048–1.143) [*]
Woynarowski et al.(2013)	audiovisual	18ASD, 18TD	11.4(2.0)	83.33%	/	0.679 (0.021–1.337) [*]
de Boer-Schellekens et al. (2013a)	audiovisual	16ASD, 16TD	19.3(1.3)	68.75%	subgroup [*]	0.723 (0.024–1.421) [*]
Summary (multisensory; N of studies = 4): Hedges' g = 0.724, 95%CI [0.431,1.018]; Z = 4.834, p < .001; I² = 0%						
de Boer-Schellekens et al. (2013b)	visual	35ASD, 40TD	18.8(1.3)	/	subgroup [*]	0.810 (0.343–1.277) ^{***}
Wada et al.(2015)	tactile	10ASD, 10TD	11.7(0.7)	70%	/	2.257 (1.164–3.349) ^{***}
Summary (unisensory; N of studies = 2): no subgroup analysis was conducted due to the number of available studies.						
Schizophrenia (N of studies = 8): Hedges' g = 0.906, 95%CI [0.620–1.192]; Z = 6.206, p < .001; I² = 31.82%						
Stevenson et al. (2017b)	audiovisual	16SCH, 16HC	42.3(8.9)	50%	/	1.384(0.628–2.140) ^{***}
Foucher et al.(2007)	audiovisual	30SCH, 33HC	33.0(9.0)	70%	223	0.942(0.427–1.457) ^{***}
Summary (multisensory; N of studies = 2): no subgroup analysis was conducted due to the number of available studies.						
de Boer-Schellekens et al. (2014)	visual	16SCH, 16HC	40.0(8.1)	93.8%	693.7	0.744(0.045–1.444) [*]
Giersch et al.(2009)	visual	19SCH, 19HC	30.6(6.1)	68.4%	243	0.845(0.194–1.496) [*]
Schmidt et al. (2011)	visual	20SCH, 11HC	30.2(8.6)	60%	525.5	1.824(0.976–2.673) ^{***}
Capa et al.(2014)	visual	20SCH, 20HC	37.2(9.2)	70%	231	0.868(0.231–1.504) ^{**}
Lalanne et al.(2012)	visual	18SCH, 18HC	35.7(6.3)	50%	275	0.714 (0.054–1.374) [*]
Grimsen et al.(2013)	visual	18SCH, 15HC	33.2(7.6)	77.78%	849.6	0.252(–0.419–0.924)
Summary (unisensory; N of studies = 6): Hedges' g = 0.832, 95%CI [0.470–1.194]; Z = 4.504, p < .001; I² = 39.76%						

SCH, schizophrenia patients; HC, healthy controls; ASD, participants with autism spectrum disorders; TD, typically developing participants.

Eq CPZ, dosage in chlorpromazine equivalent; subgroup*: Only a subgroup of ASD children were taking various kind of medications.

* p < .05.

** p < .01.

*** p < .001.

studies can be found in Table 2. All except de Boer-Schellekens et al. (2013b)'s study provided gender information. Seven of the SSD studies provided the mean dosage in chlorpromazine equivalence and two of the ASD studies reported that a subgroup of ASD children were taking different kinds of medications(de Boer-Schellekens et al., 2013a, b). Most studies stated that there was no comorbidity in the patient groups, but five studies did not include this information (Giersch et al., 2009; Noel et al., 2017; Stevenson et al., 2014, 2017b; Wada et al., 2015).

3.2. Effect sizes

Table 2 presents the meta-analysis results of all studies on schizophrenia patients and ASD patients. For schizophrenia patients, the pooled effect size for the difference in (multi-)sensory temporal function was Hedges' g = 0.91 (95% CI [0.62–1.19]; Z = 6.21, p < .001). For ASD patients, the pooled effect size was Hedges' g = 0.85 (95% CI [0.54–1.15]; Z = 5.39, p < .001). Our results indicated the presence of

impaired temporal processing and extended TBW in both clinical populations. Further, as indicated by the Z test ($Z_{\text{diff}} = 0.28, p = .78$; 95% CI of the difference $[-0.36, 0.48]$), the impairment of temporal acuity was comparable between schizophrenia patients and ASD patients.

3.3. Publication bias

Using an alpha level of .05, the fail-safe N for schizophrenia was 113, which indicated 113 unpublished studies with non-significant results were needed to nullify the observed effect. Begg & Mazumdar's test did not suggest asymmetry of the funnel plot (Kendall's Tau with continuity correction: $\tau = 0.04$; $Z = 0.12$; $p = 0.90$, 2-tailed), and this was further confirmed by the trim and fill procedure, as no imputed study was needed to be filled for adjustment.

For ASD patients, 69 unpublished studies with non-significant results were needed to nullify the observed effect. Although the number was much smaller compared with schizophrenia patients, it was acceptable as it exceeded $5K + 10$ ($=45$). Begg & Mazumdar's test suggested symmetry of the funnel plot (Kendall's Tau with continuity correction: $\tau = 0.13$; $p = .71$, 2-tailed), and the trim and fill procedure indicated no study was needed to be trimmed or filled.

3.4. Heterogeneity, subgroup analysis and meta-regression

In the eight studies on schizophrenia patients, statistical heterogeneity between studies was negligible ($\chi^2 = 10.27$, $df = 7$, $p = 0.17$; $I^2 = 31.82\%$; $T^2 = 0.054$). Combining the six unisensory (visual) temporal processing studies yielded a statistically significant pooled effect size of Hedges' $g = 0.83$ (95%CI[0.47–1.19]; $Z = 4.50$, $p < .001$), which was also homogeneous ($\chi^2 = 8.30$, $df = 5$, $p = .14$; $I^2 = 39.76\%$; $T^2 = 0.08$). As only two studies have focused on audiovisual temporal binding in SSD, we only reported the individual results of these two studies. Specifically, Foucher et al. (2007) found impaired ability to detect audiovisual asynchrony in schizophrenia patients with a large effect size (Hedge's $g = 0.94$ (95%CI [0.43–1.46], $p < .001$). Similarly, Stevenson et al. (2017a) demonstrated an extended audiovisual TBW in patients with schizophrenia compared with healthy controls (Hedge's $g = 1.38$ (95%CI [0.63–2.14]), $p < .001$). Meta-regression analyses did not yield any significant relationship between effect sizes and patients' age ($Z = 0.02$, $p = .98$) or gender ($Z = -1.29$, $p = .20$). For the seven studies reporting medication information, antipsychotic medication dosage was not significantly correlated with the effect sizes ($Z = -0.83$, $p = .41$).

In ASD patients, no significant heterogeneity was detected among the six studies ($\chi^2 = 7.57$, $df = 5$, $p = .18$; $I^2 = 33.91\%$; $T^2 = 0.05$). Splitting the studies into different subsets according to the sensory modalities, ASD patients showed enlarged audiovisual multisensory TBW indicated by the medium to large pooled effect size of four studies (Hedges' $g = 0.72$, 95%CI[0.43,1.02]; $Z = 4.83$, $p < .001$). Furthermore, this subset of multisensory studies showed no statistical heterogeneity ($\chi^2 = 0.51$, $df = 3$, $p = .92$; $I^2 = 0\%$; $T^2 = 0$). This result was consistent with two relevant studies which were only included in our systematic review reporting approximately double-sized audiovisual TBW in children with ASD compared with typically developing children (Foss-Feig et al., 2010; Kwakye et al., 2011). For unisensory studies ($n = 2$), de Boer-Schellekens et al. (2013b) reported impaired visual temporal acuity in ASD patients (Hedge's $g = 0.81$, 95%CI [0.34–1.28]) and the remaining tactile temporal processing study was an outlier with an extremely large effect size (Hedges' $g = 2.26$, 95%CI [1.16,3.35]) (Wada et al., 2015). A further examination of other studies included in our review indicated inconsistent findings of unisensory temporal acuity in ASD. Specifically, Kwakye et al. (2011)'s and Falter et al. (2012)'s study demonstrated intact and improved visual temporal acuity in ASD compared with their matched controls respectively. Meta-regression analyses indicated that the impairment of temporal acuity in ASD patients was not significantly correlated with age ($Z = -0.36$,

$p = .72$) or gender ($Z = 1.21$, $p = .23$).

For all of the 14 included studies, neither publication year nor age of the patients was not significantly associated with the effect sizes ($Z = -0.20$, $p = .84$; $Z = 0.20$, $p = .85$, respectively). Excluding the de Boer-Schellekens et al. (2013b)'s study which did not provide any gender information, no significant relationship was found between gender ratio and the severity of impairment ($Z = -0.06$, $p = .95$).

4. Discussion

To our knowledge, this is the first meta-analysis to quantify the deficits of sensory temporal integration in ASD and SSD patients. Our study provides three main insights. First, impairment of sensory temporal integration is robust in both SSD (Hedges' $g = 0.91$) and ASD (Hedges' $g = 0.85$), with comparable abnormalities observed in these two clinical groups ($p > .05$). Such impairment appears to be independent of patients' demographic characteristics (i.e., age and gender) and medication dosage. Secondly, multisensory temporal dysfunction indexed by enlarged audiovisual TBWs was consistently found in both SSD and ASD patients. Finally, in contrast to multisensory processing, whether unisensory temporal processing is impaired in ASD remains inconclusive due to the heterogeneity observed in the available studies.

4.1. Deviances of sensory temporal acuity in ASD

Irrespective of the task used, ASD patients showed a broadened TBW. However, given the inconsistent findings of unisensory temporal function in ASD, we need to identify the specific patterns of temporal acuity within each sensory modality. Apart from the auditory and visual modalities, more emphasis should also be placed on tactile processing in ASD. Our results indicated a strong effect of impaired tactile temporal acuity (Wada et al., 2015) and also an enlarged visual-tactile TBW (Greenfield et al., 2015) in ASD patients. It has been reported that atypical tactile perception can correctly discriminate autistic children from typically developing controls (Silva et al., 2015) and also predict poorer non-verbal communication skills and social impairment in ASD population (Foss-Feig et al., 2012). Moreover, less efficient visual-tactile integration indicated by diminished susceptibility to rubber hand illusion has been associated with deficits in empathy in ASD (Cascio et al., 2012).

Another unresolved question is whether there is any specific contribution of multisensory temporal deficits that cannot be predicted by individual sensory performances in ASD patients. Although some studies have demonstrated unisensory temporal abnormalities across different modalities (visual: de Boer-Schellekens et al., 2013b; auditory: Kwakye et al., 2011; tactile: Greenfield et al., 2015; Wada et al., 2015) in ASD, others have indicated unique multisensory deficits with spared (Stevenson et al., 2014) or even improved (Falter et al., 2012) unisensory temporal acuity. The third important question is whether the multisensory temporal dysfunction is only restricted to speech stimuli (de Boer-Schellekens et al., 2013a; Noel et al., 2017; Stevenson et al., 2014) or is extended/generalized to other non-speech stimuli (de Boer-Schellekens et al., 2013b; Foss-Feig et al., 2010). Despite the controversies mentioned above, a consistent, perhaps more important finding is that no matter what type of audio-visual stimuli are used, multisensory integration and temporal acuity is strongly associated with autistic symptom severity (Brandwein et al., 2014), and other higher-level abilities including attention and communication (Woynarowski et al., 2013), receptive language skills (Patten et al., 2014) especially in noisy environments (Stevenson et al., 2017b) and reward learning (Thye et al., in press). Recent research has also begun to examine the relationship between multisensory temporal function and language skills in members of the general population with autistic-like traits, whose results indicate individuals with elevated autistic traits tend to have poorer temporal adaptation for natural audio-visual

stimuli (Donohue et al., 2012). Although initially encouraging, much work is needed to obtain a more complete picture verifying the correlations between multisensory tasks and the various diagnostic features of ASD. The underlying mechanisms through which sensory deficits could impact on social and communication functions need to be further investigated.

4.2. Deviances of sensory temporal acuity in SSD

As shown by our subgroup analysis of different sensory modalities, schizophrenia patients may have generalized temporal dysfunctions ranging from unimodal sensory (especially for visual stimuli) (Haß et al., 2017; Lalanne et al., 2012; Martin et al., 2013; Stevenson et al., 2017a). It has been suggested that multisensory impairment may simply be the result of the unisensory dysfunctions observed in schizophrenia. While Stevenson et al. (2017a) has demonstrated additional multisensory temporal dysfunction not attributable to diminished unisensory temporal acuity in schizophrenia patients, some studies have reported intact or improved multisensory integration in schizophrenia patients (Grimsen et al., 2013; Stephen et al., 2013; Stone et al., 2011). Thus similar to ASD, an important issue is whether there is any multisensory deficits beyond unisensory deficits in schizophrenia. It is also important to identify whether such decreased temporal acuity in schizophrenia patients is generalized to all audio-visual stimuli or limited in semantic conditions.

In addition to sensory dysfunction, schizophrenia patients also have distortions in time perception. Patients with schizophrenia are less accurate in estimating the passage of time ranging from milliseconds (automatic timing) to several minutes (cognitively controlled timing) (Ciullo et al., 2016). They also have a more variable internal clock manifesting as greater variability in interval estimation (Thoenes and Oberfeld, 2017). A disruption of the striato-thalamo-cortical circuits may serve as the neural substrate of impaired temporal processing in schizophrenia patients (Ward et al., 2012). Furthermore, there is an overlap between the neural circuits engaged in time perception and cognitive control (Alústiza et al., 2016), suggesting the potential of interval timing as a window to investigate cognitive impairment in schizophrenia (Ward et al., 2012).

In the context of multisensory temporal integration, few studies have specifically investigated multisensory TBW in SSD, but some preliminary studies have provided interesting results. Foucher et al. (2007) suggested that a larger audiovisual TBW in schizophrenia was associated with disorganization symptoms measured by the PANSS. Using the McGurk task with different SOAs, patients with schizophrenia reported audiovisual speech to be synchronized for longer than healthy controls (Martin et al., 2013). Moreover, such explicit judgement was less predictive of “actual” implicit McGurk fusion, suggesting deficits of “structuring events in time” in schizophrenia patients (Martin et al., 2013). Stevenson et al. (2017a) similarly reported that an enlarged multisensory TBW, which was not fully explained by unisensory dysfunction, was significantly associated with clinical measures of hallucination severity in schizophrenia. Using the Sound-induced Flash Illusion Task, Haß et al. (2017) revealed that schizophrenia patients integrated temporally distant auditory stimuli to a higher degree and perceived more double-flash illusions in conditions with longer SOAs than healthy controls. However, no correlation was found between such a widened audiovisual TBW and clinical symptoms or antipsychotic dosage (Haß et al., 2017). Moreover, Ferri et al. (2017) have extended the research to subclinical populations with high cognitive-perceptual schizotypy. They found that a larger auditory-tactile TBW was correlated with higher levels of schizotypy, and that this correlation was mediated by cortical excitation/inhibition balance and fMRI resting state activity in the auditory cortex. These findings support the hypothesis that multisensory integration may be fundamental for the construction of holistic cognitive representations, and thus abnormal binding may cascade into incoherent perceptions and clinical symptoms

like auditory hallucinations and disorganized behaviour. Further research is needed to establish the association between multisensory temporal integration and schizophrenia symptoms, especially those strongly dependent on coherent perception of the inner and external world, such as hallucinations, delusions and self-disturbance (Borda and Sass, 2015; Postmes et al., 2014).

Finally, a further examination of the characteristics of patients shows that most studies only involved stabilized chronic schizophrenia patients rather than first-episode adult patients, let alone high-risk samples or adolescents with childhood-onset schizophrenia. To avoid the confounding influences of illness duration and medications, future studies should extend research to the whole schizophrenia spectrum and directly compare the multisensory temporal integration between homogeneous subgroups within this spectrum.

4.3. Future direction and implications for multisensory temporal binding in ASD and SSD

4.3.1. Commonalities and differences of TBW enlargement in ASD and SSD

This meta-analysis demonstrates robust and comparable temporal integration impairment indexed by extended TBWs in both ASD and SSD, adding evidence to support that these two neurodevelopmental disorders may share considerable overlap. Our results also complement a recent review suggesting that altered multisensory TBW is closely related to neurodevelopmental disorders (Wallace and Stevenson, 2014).

For multisensory integration, both ASD and SSD have demonstrated reduced temporal acuity, and the impairment is more prominent in the linguistic context for both clinical groups (see reviews, Baum et al., 2015; Tseng et al., 2015). When using non-linguistic stimuli, patients with schizophrenia may report an intact multisensory facilitation effect (Boer-Schellekens et al., 2014; Stephen et al., 2013; Stone et al., 2011). Similar findings have also been found in ASD patients for which impaired multisensory temporal integration is only restricted to speech-related stimuli (Bebko et al., 2006; Stevenson et al., 2014). However, in the context of unisensory processing, there are some diametric profiles between ASD and SSD. Evidence supports spared or even superior unisensory acuity in ASD (Falter et al., 2012; Happé and Frith, 2006; Mottion et al., 2006, 2009) but significant impairment in schizophrenia (unisensory temporal dysfunction: Hedges' $g = 0.83$ (95%CI [0.47–1.19], $p < .001$). Besides the unisensory temporal dysfunction indicated by our results, schizophrenia patients has been shown to exhibit generalized deficits in unisensory processing, ranging from impaired visual (Butler and Javitt, 2005), auditory (Turetsky et al., 2009), olfactory (Atanasova et al., 2008) to somatosensory (Huang et al., 2010) perception. The above evidence from unisensory processing lends support to one of the eight models of co-occurrence put forward by Chisholm et al. (2015) – “the diametrical model”, which suggests that ASD and SSD are associated with opposing deficits in some specific cognitive and behavioural domains (e.g., under- versus over-mentalizing, local versus global processing in ASD and paranoid schizophrenia) (Chisholm et al., 2015). Here, improved versus diminished unisensory temporal acuity in ASD and SSD adds further evidence to this “diametrical model”. If this were the case, individuals with comorbid ASD and SSD may experience fewer deficits than those with only one of the disorders. Future studies are needed to directly compare individuals with comorbid ASD and SSD and those with only one disorder in sensory/multisensory temporal function.

Another unresolved question is how to determine the unique multisensory contributions beyond individual sensory deficits if generalized processing disturbance across different perception levels including unisensory and bi-sensory is found. One possible solution is to identify and separate different factors (i.e., unisensory temporal acuity and clinical diagnosis) that predict the width of multisensory TBW (Stevenson et al., 2017a) using hierarchical multiple regressions, in which unisensory (visual and auditory) temporal performances are

included in one model and ASD or SSD diagnosis are added as a predictor in another model. If clinical diagnosis in the second model is predictive of an enlarged TBW, such results may indicate the contribution of unique multisensory dysfunction that goes beyond what can be explained by unisensory abnormalities.

4.3.2. Cascading effect of multisensory temporal processing

Some preliminary studies have reported an association between multisensory TBW and speech integration indexed by the McGurk effect (Stevenson et al., 2012, 2014), social communication skills measured by the Autism Diagnostic Observation Schedule (ADOS) in ASD populations (Woynarowski et al., 2013) and auditory hallucinations in schizophrenia (Stevenson et al., 2017a). Future research could establish large-scale correlational matrices, or use symptom network analysis (Borsboom and Cramer, 2013) to identify the associations and causal links between multisensory TBW and clinical symptoms. More emphasis should be put on symptoms like incoherent perception, communicative dysfunction, impaired social cognition and self-disturbance, as these clinical manifestations are all based on effective sensory and multisensory function. In addition, the potential of enlarged multisensory TBW as “bridging symptoms” linking ASD and schizophrenia should be further investigated to identify the possible roles played by multisensory function in this trans-diagnostic symptom network.

4.3.3. A spectrum perspective: does multisensory temporal impairment extend to schizotypal and autistic populations?

Schizotypal (Johns and Van Os, 2001) and autistic traits (Constantino and Todd, 2003) exist on a continuum of severity in the general population. Individuals with high levels of schizotypy have a heightened risk for the development of schizophrenia (Barrantes-Vidal et al., 2015), and exhibit poor perceptual, cognitive and motor functioning (Ettinger et al., 2015). Likewise, autistic-like individuals tend to have attenuated sensory processing abnormalities (Robertson and Simmons, 2013), intellectual disability (Hoekstra et al., 2009) and social impairment (Constantino and Todd, 2005) similar to ASD patients.

From a spectrum perspective, multisensory temporal impairment may extend to these subclinical groups. However, few studies have investigated the characteristics of multisensory temporal function in schizotypal individuals (Ferri et al., 2017) or autistic-like individuals (Donohue et al., 2012). Studies focusing on these subclinical individuals may have implications for the aetiology, early identification and intervention of these psychiatric disorders.

4.3.4. Possible therapeutic tools for multisensory plasticity

Perceptual training with feedback has been shown to successfully narrow the width of TBW (Powers et al., 2009, 2016; Schlesinger et al., 2014; Stevenson et al., 2013), accompanied by increased neural network plasticity centred on the posterior superior temporal sulcus (Powers et al., 2012). Moreover, individuals who seem to benefit most are those whose TBWs are the largest before training (Powers et al., 2009; Stevenson et al., 2013). Apart from evidence from university students and young adults (Powers et al., 2009, 2012, 2016; Schlesinger et al., 2014; Stevenson et al., 2013), such reduction in the width of the TBW has also been observed in older adults after temporal discrimination training (Setti et al., 2014). More evidence supporting the experience-dependent plasticity of multisensory temporal integration comes from musically trained individuals whose audiovisual TBW is much shorter than non-musicians (Bidelman, 2016). Given the plasticity of the TBW and its association with higher-order cognitive abilities, perceptual training to narrow the width of TBW may provide a new therapeutic tool in both neurodevelopmental disorders.

However, longitudinal studies are needed to examine the durability of the training benefit. It is also important to evaluate higher-level changes that go beyond the trained task. A recent study conducted with university students found that the effect of audiovisual simultaneity judgement training could not be generalized to other multisensory

tasks, but could result in improvements in unisensory (visual) temporal acuity (Powers et al., 2016). Another interesting study demonstrated that a shortened TBW after perceptual training was accompanied by improved ability to detect auditory changes in pulse oximetry in a group of resident anaesthesiologists (Schlesinger et al., 2014). Given the inconsistent findings and limited number of available studies, future research is needed to further examine the generalization effect of multisensory temporal training. These higher-order changes can be evaluated using (semi-)structured interviews, such as the Autism Diagnostic Observation Schedule (ADOS, Lord et al., 1989), to identify the beneficial effect of perceptual training on language skills and social interactions. It may also be promising to conduct functional imaging studies to examine the malleability of multisensory network and other cognitive networks in clinical samples. Only if the “narrowing of TBW” effect were durable and stable and could result in improvement in other clinical symptoms can we consider such perceptual training as promising and practical in clinical contexts.

4.4. Limitations

This study has several limitations. First, the studies included in the meta-analysis were heterogeneous in terms of experimental paradigms used to estimate the width of the TBW. Secondly, reporting bias may exist in both individual studies and reviews. For individual studies, only a small proportion of included studies had an adequate sample size and used enough trials per SOA to estimate the TBW. For reviews, we were unable to retrieve complete sets of data from all the identified research (seven papers were excluded from our meta-analysis due to insufficient data). Thirdly, the influence of illness duration and comorbidities have not been fully examined, as some studies did not provide sufficient information. Finally, it should be noted that the available studies is relatively limited and the robustness of the present results should be interpreted cautiously.

4.5. Conclusions

Decreased temporal acuity indexed by an enlarged TBW is a common feature in both schizophrenia and ASD. While controversies still exist with regard to unisensory temporal function, consistent and robust impairment of higher-level “multisensory temporal integration” is demonstrated in both neurodevelopmental disorders. Such multisensory dysfunction is further found to be associated with clinical symptoms like hallucinations, impaired social communications and self-disturbance. Future studies should examine the specific mechanisms of prolonged TBW. Perceptual training that shortens prolonged TBW may be promising interventions to alleviate schizophrenia and autistic symptoms.

Acknowledgments

This study was supported by a grant from, Beijing Municipal Science & Technology Commission Grant (Z161100000216138), National Key Research and Development Programme (2016YFC0906402), Beijing Training Project for Leading Talents in S&T (Z151100000315020), the CAS Key Laboratory of Mental Health, Institute of Psychology, and the CAS/SAFEA International Partnership Programme for Creative Research Teams (Y2CX131003). No conflict of interest to be declared.

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