



Review article

Ripe for solution: Delayed development of multisensory processing in autism and its remediation

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ABSTRACT

Difficulty integrating inputs from different sensory sources is commonly reported in individuals with Autism Spectrum Disorder (ASD). Accumulating evidence consistently points to altered patterns of behavioral reactions and neural activity when individuals with ASD observe or act upon information arriving through multiple sensory systems. For example, impairments in the integration of seen and heard speech appear to be particularly acute, with obvious implications for interpersonal communication. Here, we explore the literature on multisensory processing in autism with a focus on developmental trajectories. While much remains to be understood, some consistent observations emerge. Broadly, sensory integration deficits are found in children with an ASD whereas these appear to be much ameliorated, or even fully recovered, in older teenagers and adults on the spectrum. This protracted delay in the development of multisensory processing raises the possibility of applying early intervention strategies focused on multisensory integration, to accelerate resolution of these functions. We also consider how dysfunctional cross-sensory oscillatory neural communication may be one key pathway to impaired multisensory processing in ASD.

1. Introduction

Humans and animals have evolved an exquisitely sensitive and highly diverse repertoire of sensory receptors to sample the multiple sources of energy available in our environment. In turn, neural plasticity during development allows the neural architecture of the infant brain to learn to combine and integrate these sources of information in ways that enhance performance and improve survival (Wallace et al., 2006). Thus, measures of task performance under multisensory conditions show that multiple species can take advantage of the often complementary or redundant sensory information available to them in their environment (Bahrick and Lickliter, 2000; Foxe and Simpson, 2002; Gibson, 1969; Hammond-Kenny et al., 2016; Stein et al., 1996), allowing them to evolve and adapt to novel ecological niches (Karageorgi et al., 2017). In the case of humans, watching lip and facial movements, hand gestures, head nods, facial configurational (Jaekl et al., 2015) and even feeling the breath of a speaker on your skin (Gick and Derrick, 2009) can all provide additional information to an observer trying to understand what a speaker is saying to them (Ma et al., 2009; Ross et al., 2011; Ross et al., 2007a; Sumbly and Pollack, 1954). Even for

more basic non-speech stimulus configurations, hearing a sound produced by a visual object is likely to enhance its detectability (Fiebelkorn et al., 2011; Molholm et al., 2002; Van der Burg et al., 2008). Simply put, through binding of multiple sensory inputs in the nervous system, multisensory integration (MSI) allows one to form higher fidelity representations of the environment, which in turn promote adaptive behavior (Molholm and Foxe, 2010; Stein, 1998).

Congruent multisensory inputs tend to enhance task-relevant performance when compared to circumstances under which solely unisensory input is made available (Giard and Peronnet, 2006; Molholm et al., 2002; Talsma and Woldorff, 2005; Teder-Sälejärvi et al., 2002), with performance often exceeding linear predictions based on unisensory processing. When these integrative behavioral patterns are observed, they are also generally reflected in nonlinear neural responses, i.e. multisensory integration (MSI) (Beauchamp et al., 2010; Butler et al., 2016; Foxe et al., 2000; Foxe and Schroeder, 2005; Meredith and Stein, 1983; Molholm et al., 2002). There are multiple parallel and hierarchically organized processing stages in the brain at which multisensory information may interact to affect sensory-perceptual and motor processes (Driver and Noesselt, 2008; Rohe and

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Noppeney, 2016), such as stimulus detection, localization, identification, and action planning (Fiebelkorn et al., 2013; Lucan et al., 2010; Mercier et al., 2015; Nath and Beauchamp, 2012). An important consideration pertains to the variable timing of neural transmission through the early hierarchical stages of the initially segregated sensory processing streams. Inputs arriving at the separate sensory epithelia (e.g. the skin, the hair cells in the cochlea, the retina) must be “tagged” by the central nervous system as belonging together in the face of varying transmission times from sensory receptors to subcortical regions and on into cortex. In turn, information that is represented in anatomically segregated brain regions must be communicated across significant cortical distances, perhaps involving multisynaptic cascades that propagate across several intervening functional regions, but possibly also via mono-synaptic long-range inter-regional connections (Falchier et al., 2010; Foxe and Schroeder, 2005; Keniston et al., 2010; Rockland and Ojima, 2003). Given the multiple processes that MSI must be built upon, which require long-range network integrity and functionality, it is a reasonable proposition that MSI may be particularly vulnerable to insult. Indeed, MSI has been shown to be impaired in a number of complex neurodevelopmental and neuropsychiatric disorders, such as dyslexia (Francisco et al., 2017; Hahn et al., 2014), schizophrenia (Ross et al., 2007b) and rare lysosomal storage disorders (Andrade et al., 2014), to mention just a few. As we will elaborate below, however, it is ASD in particular that has been most extensively investigated and associated with dysfunction in MSI processing.

Cardinal symptoms of autism spectrum disorder (ASD) include deficits in social interaction, and restricted interests and repetitive behaviors (APA, 2013). These are often accompanied by hypo- or hypersensitivity to sound, light, and touch (Kanner, 1943; Kern et al., 2006). It has long been proposed, based on clinical evaluations and parental observations, that dysfunction in multisensory integration may be a significant component of the sensory atypicalities and social communication deficits seen in ASD (Ayres and Tickle, 1980; Iarocci and McDonald, 2006; Martineau et al., 1992; Molholm and Foxe, 2010). In what follows, we assess the current state of knowledge regarding MSI in autism, focusing specifically on the impact of development on these processes, and on audiovisual paradigms for which there is a substantial literature. It should be pointed out that these studies all involve individuals with largely normal range IQs (this is often necessary for task performance, and also allows for comparison with a typically developing control group), and thus generalization should be limited to high functioning individuals on the autism spectrum. In turn, we consider how naturally occurring training may serve to improve MSI function in ASD, and how this can be leveraged to shift improvements in function to earlier stages of development. Finally, we forward a possible mechanistic account of altered MSI in ASD. For easy reference, Table 1 presents a list of studies that we cite here on multisensory processing in ASD, along with a brief summary of the study paradigms and major findings.

1.1. Multisensory integration in autism: a developmental perspective

The development of multisensory processing and integration has been meticulously investigated in animal models, primarily through electrophysiological recordings in the superior colliculus (SC; see (Meredith and Stein, 1983)). This midbrain structure is involved in rapid orienting responses, and contains both bisensory and trisensory neurons that receive combinations of auditory, visual, and somatosensory inputs (Meredith and Stein, 1986). From these studies, we have learned that the organism’s specific experiences with the multisensory environment significantly influence the development of MSI. For example, while there are neurons present in the SC at birth that respond to more than one channel of sensory input, these cells do not initially show integrative, non-linear, responses. Rather, MSI properties develop only after experience with multisensory cues has been gained (Wallace et al., 2004; Wallace and Stein, 1997, 2001, 2007). Wallace and Stein (2007)

provided a particularly powerful example of environmental influences on the development of MSI, showing how the natural spatial overlap of multisensory SC receptive fields for the different sensory modalities can be dramatically influenced through manipulations of the post-natal environment. Animals were raised in a sensory environment where the only auditory and visual stimuli they were exposed to, while temporally coupled, were spatially displaced from each other in a consistently mapped fashion. This led to massively altered functionality of the SC audiovisual neurons since they developed mismatched auditory and visual spatial fields such that only stimulation of the spatially disparate visual and auditory mappings generated integrative responses (Wallace and Stein, 2007).

Based on abundant evidence for early plasticity of the multisensory system in animal models, it is not surprising that developmental studies in humans also show that extensive experience is necessary before the nervous system can fully benefit from multisensory cues. Sensitivity to temporal coincidence of rhythmic audiovisual stimuli, and to the congruency of native audiovisual speech stimuli, appear to emerge already within the first year of an infant’s life (Lewkowicz, 1996, 2003; Pons et al., 2009). Yet, multisensory influences on perception and performance are nevertheless greatly reduced in young children when compared to adolescents and young adults (Brandwein et al., 2011; Burr and Gori, 2012; Ernst, 2008; Gori et al., 2012; Ross et al., 2015, 2011; Cowie et al., 2013, 2016; Greenfield et al., 2017). Several psychophysics studies found that children younger than eight years of age do not optimally integrate haptic and visual cues, but instead that prior to that point, one sense dominates the other, depending on the specific task demands (Gori, 2015; Gori et al., 2008, 2012). This protracted plasticity of multisensory processing may enable the flexible use of multisensory information. For example, the child can learn to integrate multisensory speech cues that are specific to their native language (Lewkowicz, 2014), and individuals readily adapt to changes in body schema to effectively interact with objects in their environment (Cardinali et al., 2009).

Given the prolonged trajectory of the development of multisensory processing and the extensive influence of the environment on MSI operations, MSI deficits in ASD may be best understood in a developmental context. Here we focus on audiovisual MSI in ASD, where the bulk of the relevant studies are found. We note that it is likely that the developmental course of multisensory processing, and how it is impacted in ASD, will differ somewhat as a function of the sensory modalities and the specific processes under consideration.

1.1.1. Multisensory integration of audiovisual speech

Deficits in language and socio-emotional processing are canonical symptoms of autism (APA, 2013). Audiovisual speech is a particularly rich and natural occurring multisensory signal that conveys both linguistic and extra-linguistic (including social and emotional) information, and thus it is not surprising that many studies of MSI in ASD have focused specifically on the integrity of audiovisual speech perception (Bebko et al., 2006; Irwin and Brancazio, 2014; Kujala et al., 2005; Paul et al., 2005; Silverman et al., 2010; Smith and Bennetto, 2007). In general, these studies have demonstrated multisensory speech deficits in children with autism. For example, in a cross-sectional study performed by our group (Foxe et al., 2015), we assessed the development of multisensory speech perception in individuals with and without ASD, from 7 to 19 years of age. Spoken monosyllabic words were presented in varying degrees of background noise, making them difficult to identify, and the benefit of an accompanying video of the speaker saying the word was then assessed. In this audiovisual speech-in-noise paradigm, younger children with ASD (7–12 year olds) showed severe deficits in multisensory speech perception when compared to controls (see also (Irwin et al., 2011; Stevenson et al., 2017)). Crucially, although identification of the auditory-alone words was essentially equivalent between the ASD and TD groups (i.e. unisensory processing appeared to be largely intact), individuals with ASD simply did not

Table 1

Paradigms and findings from MSI studies on ASD population. Numbers in Age column represent age range (mean \pm std), when available.

Research	# subjects	Age (range, mean \pm std)	Stimulus type	Paradigm / Task	MSI effect in ASD
Bebko et al. (2006)*	16 ASD 16 TD	4.6–6.1 (5.5 \pm 0.5) 1.7–4.2 (2.36 \pm 0.7)	Animated AV objects	Preferential looking	No group differences
Mongillo et al. (2008)*	15 ASD 21 TD	8-19 (13.7 \pm 3.9) 11-19 (13.4 \pm 2.8)	Social and nonsocial AV stimuli	Classification; Match-mismatch	Social stimuli: impaired MSI Nonsocial stimuli: No group differences
Foss-Feig et al. (2010)	29 ASD 17 TD	8-17 (12.6 \pm 2.6) 8-17 (12.1 \pm 2.2)	Flashes and beeps	SiFi	Wider TWIN for ASD
Russo et al. (2010)	17 ASD 17 TD	6-16 (10.4 \pm 2.7) 6-16 (10.5 \pm 2.9)	Vibrations and tones	No task	EEG: impaired MSI
Kwayke et al. (2011)	35 ASD 27 TD	8-17 (12.2 \pm 2.7) 8-17 (11.7 \pm 2.4)	Discs and clicks	TOJ	Wider TWIN for ASD
Brandwein et al. (2013)	46 ASD 72 TD	7-10 (9.2 \pm 1.3; 9 \pm 1.2) 11-16 (13 \pm 1.6; 13.8 \pm 1.6)	Discs and beeps	SD	Both age groups: Behavior: impaired MSI EEG: Reduced neural integration
Irwin and Branzcizio (2014)*	10 ASD 10 TD	5.6-15.9 (10.2 \pm 3.1) 7-12.6 (9.6 \pm 2.4)	Beeps and shapes	Gaze patterns for AV videos	No group differences
Brandwein et al. (2014)	52 (ASD only)	6-17 (11.2 \pm 2.9)	Discs and beeps	SD	Behavior: impaired MSI; EEG: correlation between AV modulation and ADOS scores
Stevenson et al. (2014a)	31 ASD 31 TD	6-18 (12.1 \pm 3.1) 6-18 (11.9 \pm 2.9)	Flashes and beeps	SiFi	Greater susceptibility to the SiFi
Stevenson et al. (2014b)*	32 ASD 32 TD	6-18 (11.8 \pm 3.2) 6-18 (12.3 \pm 2.3)	Flashes and beeps Tools	SJ	No difference in TWIN for non-speech stimuli
Noel et al. (2016)*	26 ASD 26 TD	7-17 (12.3 \pm 3.1) 8-17 (11.6 \pm 3.8)	Flashes and beeps Tools	SJ	Wider TWIN; Impaired recalibration
Van der Smagt et al. (2007)	15 ASD 15 TD	20.5 \pm 3.2 20.7 \pm 2.6	Flashes and beeps	SiFi	No group differences
Keane et al. (2010)*	6 ASD 6 TD	19-47 (30 \pm 9) 18-49 (30 \pm 8)	Flashes and beeps	Cross-modal dynamic capture; SiFi	No group differences
De Boer-Schellekens et al., (2013)	35 ASD 40 TD	15-24 (18.8 \pm 2.1) 15-24 (18.8 \pm 1.3)	Clicks and flashes	Pip and Pop Digital clock reading task	No group differences
Collignon et al. (2013)	19 ASD 20 TD	14-31 (24.5 \pm 5) 14-27 (21 \pm 4)	Lines and tones	Pip and Pop	No group differences
Poole et al. (2016)	18 ASD 18 TD	31 \pm 8.4 31 \pm 8.7	Vibrations, beeps, flashes	TOJ	No group differences for size of JND and PSS in any modality pairing
Turi et al. (2016)	16 ASD 16 TD	17-34 (29.2 \pm 5.2) 18-31 (27 \pm 2.8)	Flashes and beeps	SD	No group differences for TWIN No recalibration
Bao et al. (2017)	20 ASD 20 TD	13-29 (18.7 \pm 4.7) 13-28 (18 \pm 9.5)	Flashes and beeps	SiFi	No group effect on fission illusion Larger susceptibility to the fusion illusion

Speech Stimuli

de Gelder et al. (1991)	17 ASD 17 TD	6.5-16.3 (10.9 \pm 2.3) 6.8-11.1 (8.5 \pm 1.3)	McGurk	McGurk illusion: report which syllable was perceived.	Reduced MSI
Williams et al. (2004)	15 ASD 15 TD	5-13 (8.8 \pm 1.4) 5-13 (9.5 \pm 1)	McGurk	McGurk illusion: report which syllable was perceived	No difference when corrected for visual only
Bebko et al. (2006)*	16 ASD 16 TD	4.6–6.1 (5.5 \pm 0.5) 1.7–4.2 (2.36 \pm 0.7)	AV speech	Preferential looking	Impaired MSI: altered gaze patterns
Smith and Bennetto (2007)	18 ASD 19 TD	12.4-19.5 (15.8 \pm 2.2) 12-19.2 (16 \pm 2)	AV Speech in noise	Speech in noise	Impaired MSI
Mongillo et al. (2008)*	15 ASD 21 TD	8-19 (13.7 \pm 3.9) 11-19 (13.4 \pm 2.8)	McGurk	McGurk illusion: report which syllable was perceived.	Impaired MSI
Silverman et al. (2010)	19 ASD 20 TD	12-18 (15.3 \pm 0.5) 12-18 (15.2 \pm 0.4)	AV Speech and gestures	Speech-and-Gesture	Reduced multisensory benefit for gestures
Taylor et al. (2010)	24 ASD 30 TD	7.9-16.4 (12.6 \pm 2.4) 8.3-16.4 (11.8 \pm 2.5)	McGurk	McGurk illusion: report which syllable was perceived	Impaired MSI of speech at young age; Amelioration over age for ASD group
Irwin et al. (2011)	13 ASD 13 ASD	5-15 (9.1) 7-12 (9.2)	AV consonant–vowel syllables	Lip-reading; Speech in noise; McGurk illusion: report which syllable was perceived	Lip-reading: impaired performance for ASD Speech in Noise: No group differences McGurk: Impaired MSI in ASD
Wojnarosky et al. (2013)	18 ASD 18 TD	8-17 (12.3 \pm 2.6) 8-17 (11.5 \pm 1.9)	McGurk	McGurk illusion: report which syllable was perceived	No group effect on McGurk; Wider TWIN (marginal effect)
Irwin and Branzcizio (2014)*	10 ASD 10 TD	5.6-15.9 (10.2 \pm 3.1) 7-12.6 (9.6 \pm 2.4)	AV consonant–vowel syllables	Speech in Noise; gaze patterns	Altered gaze patterns for ASD in multisensory conditions
Bebko et al. (2014)	15 ASD 19 TD	6.6-14.6 (10.5 \pm 2.5) 6-15.6 (10.2 \pm 2.7)	McGurk	McGurk illusion: report which syllable was perceived	Impaired MSI
Stevenson et al. (2014b)*	32 ASD 32 TD	6-18 (11.8 \pm 3.2) 6-18 (12.3 \pm 2.3)	McGurk	SD	Wider TWIN for ASD
Foxe et al. (2015)	84 ASD 142 TD	5-6 (6; 5.6) 7-9 (8 \pm 0.9; 8 \pm 0.6) 10-12 (11.4 \pm 0.7; 10.9 \pm 0.8) 13-15 (14.1 \pm 0.8; 13.4 \pm 0.7) 16-17 (16.7 \pm 0.5; 16.8 \pm 0.5).	AV Speech in noise	Speech in noise; repeat the perceived words	Impaired MSI in the 7-9 group Full resolution in the 13-15 group
Noel et al. (2016)*	26 ASD 26 TD	7-17 (12.3 \pm 3.1) 8-17 (11.6 \pm 3.8)	AV consonant–vowel syllables	SD	No group differences
Keane et al. (2010)*	10 ASD 9 TD	19-47 (30 \pm 9) 18-49 (30 \pm 8)	McGurk	McGurk illusion: report which syllable was perceived	No group differences

Table 1 (continued)

Children and adolescents (<18)
Adults (>18)
Mixed age group

Abbreviations: ASD, autism spectrum disorder; TD, typically developed; MS multisensory; SiFi, Sound Induced Flash Illusion; TWIN, time window of integration; JND, Just Noticeable Difference; PSS, Point of Subjective Simultaneity; SOA, Stimulus Onset Interval; SD, Speeded Detection; A, auditory; V, visual; AV, audiovisual; TOJ, temporal order judgment; SJ, Simultaneity judgment; JND, just noticeable difference; EEG, encephalogram;

*Studies that use both Speech and Non-speech stimuli, and appear in both sections in the table.

benefit from the addition of the video to the same extent as controls. However, these multisensory deficits were not observed in the older age group (13–15 year olds), suggesting a relative amelioration of audiovisual speech integration by the teenage years. In typical development there is a progressive increase in the integration of audiovisual information to enhance speech perception (Ross et al., 2011). The findings of Foxe et al. suggest a similar, albeit significantly delayed, developmental increase in the ability to benefit from multisensory inputs in children with autism. Interestingly, while Stevenson et al. (2017) also found MSI deficits in ASD at the whole word level for a group of 6–18 year olds, when they instead considered the number of phonemes correctly identified, MSI gain did not significantly differ between ASD and control groups. The absence of group differences in multisensory gain at the phonemic level of analysis might suggest that such multisensory deficits are only seen for higher levels of speech processing, where lexical information is relevant. This explanation, however, is not consistent with data from the so-called McGurk speech illusion, described below, in which reduced MSI in children with autism is found for phonemic-level inputs.

In the McGurk illusion, mismatched auditory (phonemes) and visual (visemes) speech components are presented and an illusory speech sound is perceived (McGurk and Macdonald, 1976; Saint-Amour et al., 2007). By manipulating the congruency between the visual and the auditory stimuli, the resultant percept is often a fusion of the two stimuli (for example, hearing the syllable/ba/while watching the visual lip movements of/ga/, usually results in the person perceiving the phoneme/da/). In typical development, the strength of this illusion increases with age (Hockley and Polka, 1994; Tremblay et al., 2007), presumably due to increased multisensory influences on speech perception. In children with ASD, the McGurk effect has been found, in the majority of cases, to be significantly reduced compared to age matched TD controls (Bebko et al., 2014; De Gelder et al., 1991; Iarocci et al., 2010; Irwin et al., 2011; Mongillo et al., 2008; Williams et al., 2004; Woynaroski et al., 2013). Taylor et al. examined patterns of responses to McGurk stimuli (Taylor et al., 2010) in children and adolescents with and without a diagnosis of autism. They found that McGurk illusions were reduced in younger children with ASD (7–14 year olds) but that adolescents with ASD performed similarly to the control group (15–16 year olds). Similarly, Stevenson et al., 2014b examined the McGurk illusion in a group of children and adolescents, and found reduced McGurk illusions in their ASD sample. However, when the data were separated into two age groups, the pattern of findings contrasted somewhat with those of Taylor et al. with significantly fewer McGurk Illusions observed in the older ASD vs. TD group (13–18 year olds), and no statistically reliable group difference in their younger group (6–12 year olds). It is not clear what accounts for this difference in developmental findings across studies. However, consistent with Taylor et al. (2010) finding, McGurk illusions did not differ significantly between the ASD and control groups in adults (Keane et al., 2010).

Overall, findings from both the audiovisual speech-in-noise and the McGurk studies argue for substantially reduced multisensory influences on speech perception in children with ASD, with amelioration of deficits by adolescence/early adulthood. Of major interest is what drives this change. One possibility is that exposure to multisensory speech, which can be reasonably assumed to occur daily, serves to train the MSI function over time, eventually leading to recovery of function in ASD. A

critical point here is whether the same trend is observed using non-speech stimuli, such as objects and simple beeps and flashes. If a similar resolution of MSI function occurs for other types of stimuli where similar levels of exposure cannot be assumed, then a non-specific mechanism may lead to the developmental recovery of multisensory processing in ASD. For instance, the strengthening of connectivity between frontal and sensory cortices that occurs throughout adolescence (Simmonds et al., 2014), or the extensive therapies that individuals with autism frequently receive (Pickles et al., 2016), could play a role in how multisensory information is processed.

1.1.2. Multisensory integration of audiovisual non-speech stimuli

Speech and communication are specifically impaired in autism and thus might have a unique status in the developmental delay of MSI. However, studies using non-speech stimuli to test MSI in ASD have also, for the most part, found deficits in MSI in children. Multisensory integration in this domain can be assessed by testing whether an interactive or independent processing model better explains response time facilitation to redundant multisensory cues. In the non-interactive model (Miller, 1982; Raab, 1962), each stimulus of the auditory and visual pair is assumed to independently compete for response initiation, with the faster of the two mediating the response. In the interactive model (Miller, 1982; Molholm et al., 2002; Raab, 1962), an interaction between the inputs leads to enhancement of the reaction to the multisensory stimuli. If simple probability summation of the fastest responses from each of the unisensory conditions (i.e., the non-interactive model) cannot account for the response speeding, it is assumed that the inputs interacted to enhance the response to the multisensory stimulus. Using this approach, we examined the development of multisensory processing in ASD. Tone and flash stimuli were presented in unpredictable order either alone or in combination, resulting in audio alone, visual alone, and audiovisual stimuli. Participants performed a simple detection task in which they were instructed to respond with a speeded button press whenever any of the three stimulus types (auditory/visual/audiovisual) occurred. In typically developing children, behavioral multisensory effects increased as a function of age. In contrast, these multisensory effects were not present in either the younger or older group of children with ASD. Congruently, neural indices of MSI were reduced in both the younger (7–10 year olds) and the older (11–16 year olds) children with ASD, and this was correlated with autism severity (Brandwein et al., 2015; Brandwein et al., 2013). Thus, impaired MSI in ASD is not exclusive to socially relevant speech stimuli. Preliminary analysis of behavioral data from a larger cohort of ASD and TD, using the same paradigm, replicates the finding that MSI effects are delayed in children with ASD, and further suggests that adults with autism show largely typical MSI effects (Crosse et al., 2017).

Experiments using a paradigm known as the *sound-induced flash illusion* (SiFi) have also shown impaired MSI in children and adolescents with ASD for non-speech stimuli. In this illusion, a single flash is accompanied by two successive tones, and observers tend to report seeing two visual flashes, rather than the physical one (Mishra et al., 2007; Shams et al., 2000, 2002). This illusion is considered a consequence of how the sensory systems communicate to enhance information processing, with cross-sensory inputs decreasing the threshold for an evoked response (Mishra et al., 2007). Children with ASD show reduced susceptibility to this illusion relative to TD controls, with fewer reports

of illusory flashes (Stevenson et al., 2014a,b,c). Adults with autism, however, appear to be equally susceptible to the illusion when compared to controls (Bao et al., 2017; Keane et al., 2010; Van der Smagt et al., 2007) implying once again that multisensory processing is operating in a largely typical manner in adults with autism.

The findings described above are consistent with MSI resolution over age representing a general phenomenon in ASD, rather than one that is specific to audiovisual speech. There are exceptions, however, where impaired MSI is reported in adults with ASD. One example comes from the “pip-and-pop” paradigm (Van der Burg et al., 2008). Here, presentation of a temporally relevant sound (a pip) facilitates performance on a visual search task, such that the visual target pops out of a cluttered visual display. The two studies that have used this paradigm in adults with ASD report contradictory results, however. While (Collignon et al., 2013) found significant group differences due to a lack of auditory-based facilitation in their adult ASD group, De Boer-Schellekens et al. (De Boer-Schellekens et al., 2013) found equivalent facilitatory effects across adult ASD and control groups. In Collignon et al. (2013), the ASD group performed at superior levels on the visual alone condition of the task, such that performance resembled that of the control group under the multisensory condition. Individuals with ASD sometimes exhibit superior performance on visual search tasks (Shah and Frith, 1983; Shirama et al., 2016), and it is possible that this superior performance here is what accounts for the lack of an auditory facilitatory effect in Collignon et al. (2013); that is, that there was a ceiling effect of sorts. Further investigation is necessary to understand the possible role of methodological differences between the studies in accounting for the presence or absence of multisensory effects in the pip-and-pop paradigm.

Another, perhaps more compelling, example is found in studies measuring the so-called multisensory temporal window of integration (TWIN). Normally, the brain tolerates subtle time lags between the onsets of auditory and visual stimuli, perceiving stimuli that arrive asynchronously as synchronous. This tolerance may be necessary due in part to the different propagation speeds of light and sound vibrations (Mégevand et al., 2013), arriving at the retina (Berry et al., 1999) and hair cells (Corey and Hudspeth, 1979), respectively. Further, the different neural response latencies (Bushara et al., 2001) and number of processing stages (Foxe and Schroeder, 2005) are also likely to contribute to timing variability in the convergence of multisensory inputs to a given region (Molholm et al., 2006). The TWIN is most often measured using temporal order judgment (TOJ) tasks in which participants are presented with two sources of sensory stimulation, such as tones and flashes, separated by a range of stimulus onset asynchronies, and are then asked to judge their simultaneity, or, alternatively, their temporal order (i.e., “Which came first, the auditory or the visual stimulus?”). Of relevance here, these judgments are influenced by the degree and direction of asynchrony between the stimuli on the previous trials (Fujisaki et al., 2004; Vroomen et al., 2004). On average, a few minutes of exposure to an audiovisual pair with a fixed time lag (on the order of ~200 ms) leads to a shift in simultaneity judgments such that larger lags are tolerated, relative to exposure to simultaneous stimuli (Fujisaki et al., 2004). This “lag adaptation” is also shown on a trial-to-trial basis such that exposure to asynchrony on one trial leads to greater tolerance of the same order asynchrony on the next trial (Van der Burg et al., 2013).

Two studies have recently shown that individuals with ASD lack this rapid multisensory temporal recalibration, and do not adjust simultaneity judgments as a function of the temporal order of the stimuli on the previous trial. This failure to recalibrate the multisensory temporal window of integration on a trial-by-trial basis has been shown for both children and adolescents with ASD (Noel et al., 2017), as well as for adults (Turi et al., 2016), using simple, non-speech, stimuli. Notably, this same lack of adaptation has been shown in the ASD population with tasks involving complex stimuli like numbers (Pellicano et al., 2007; Turi et al., 2015) and faces (Pellicano et al., 2007), as well as more

simple scenarios such as loudness changes (Lawson et al., 2015). As such, we believe it likely that these findings reflect impaired rapid online adaptation/recalibration, rather than impaired MSI, in ASD. This adaptive impairment may operationalize a prominent feature in the clinical picture of ASD: reduced adaptation to new environments and situations, leading to distress at small changes, difficulties with transitions, and rigid thinking patterns (APA, 2013), although this clearly remains to be specifically tested experimentally.

Thus far we see that multisensory processing is impaired in children with ASD for both speech and non-speech stimuli. The weight of the evidence points to substantively intact multisensory abilities in adults with ASD for speech, whereas exceptions were found in paradigms using non-speech stimuli. One possibility is that MSI normalization in the speech domain is more robust than in non-speech areas, due to daily exposure to speech. Alternatively, these exceptions may reflect altered functioning in other information processing domains, such as temporal recalibration or visual search.

1.1.3. A potential role for adaptation/recalibration in MSI development

It has been proposed that a lack of MSI in young children may be a result of a continual sensory calibration process in the developing brain (Gori, 2015). According to this idea, during the sensory calibration period in childhood, the less accurate senses are calibrated by the more accurate sense for a given type of information (e.g., size estimates), and the redundancy in multisensory information is only translated to enhancement once this process is completed. The instantaneous calibration processes referred to above may share similar elements with this hypothesized developmental calibration, such as modification of a decision criterion after feedback. Impaired MSI in ASD might reflect one aspect of impaired inter-sensory calibration in this population. Given this scenario, appropriate training focused on adjustment to changes in multisensory surroundings could be useful to improving adaptation to new environments in autism, and might have positive consequences for other daily functions.

1.1.4. Multisensory stimuli and the temporal window of integration

Studies on the multisensory TWIN (described above), while not directly testing MSI, nevertheless pertain to the operations underlying MSI. The size of the temporal window within which multisensory stimuli are judged to occur simultaneously is often taken as the interval within which stimuli are integrated. Many studies have used the TWIN to examine the development of multisensory processing, and to consider the integrity of MSI in clinical populations. The multisensory TWIN has been measured in ASD in several studies now, using both speech and non-speech stimuli. When differences are found, individuals with ASD tend to exhibit a wider multisensory TWIN (De Boer-Schellekens et al., 2013; Foss-Feig et al., 2010; Kwakye et al., 2010; Noel et al., 2016, 2017). Such differences are typically taken to indicate reduced multisensory temporal acuity that in turn leads to less reliable binding. Indirect support for this thesis comes from Stevenson et al. (Stevenson et al., 2014a,b,c), where the percent of illusory McGurk responses negatively correlated with the width of the temporal window for binding simple audiovisual stimuli among children and adolescents with autism. However, the literature is inconclusive as to whether the multisensory TWIN in children and adolescents with ASD differs from typically developing controls. For non-speech stimuli, sometimes group differences are found (De Boer-Schellekens et al., 2013; Foss-Feig et al., 2010; Kwakye et al., 2010; Stevenson et al., 2014a,b,c), whereas other times they are not (Noel et al., 2017; Smith et al., 2017; Stevenson et al., 2017). Interestingly, two of the four studies that failed to show group differences in TWIN for non-speech stimuli, showed group differences for conditions in which speech stimuli were instead presented (Noel et al., 2017; Stevenson et al., 2014a,b,c).

In the only multisensory TWIN studies that have been conducted in adults with ASD, both of which used non-speech stimuli, judgments of temporal order for multisensory inputs were comparable between ASD

and TD participants (Poole et al., 2016; Turi et al., 2016). However, in the absence of clear TWIN differences in children and adolescents, this cannot be taken to support a developmental shift in MSI function in ASD (Poole et al., 2016; Turi et al., 2016). In all, while intriguing, we find the data on the multisensory TWIN in ASD to be somewhat inconclusive at this point.

1.2. Can we accelerate the recovery of MSI function in ASD?

The apparent amelioration of MSI deficits over the course of development in the ASD population raises the promise that controlled manipulations and educational strategies could be deployed to shift MSI recovery to earlier stages of development. Importantly, if MSI is intact at developmentally critical stages, it could positively impact the emergence of a range of functions in ASD that have been shown to be impaired, such as verbal communication. One approach to improving MSI function might be through engagement with multisensory perceptual learning tasks starting at a young age. We already know that the temporal discrimination of multisensory stimuli, which is correlated with MSI performance in ASD (Stevenson et al., 2014a,b,c) can be enhanced with training, and that such training effects can last for at least one week (Powers et al., 2009). Additional support for the efficacy of audiovisual training comes from studies in which the outcome measures is improvement in unisensory perception. For example, after training on an audiovisual matching task using shape and sound sequences, 7-year-old children with dyslexia showed improvement in reading tasks, accompanied by enhanced brain reactions as measured by EEG (Kujala et al., 2001). Multisensory training was also found to ameliorate haemianopia, i.e. blindness in half the visual field, in animals with visual cortex ablation (Jiang et al., 2015). Following lesion-induced contralateral haemianopia, the animals repeatedly performed a task in which they oriented to and approached a salient auditory cue presented to the anopic hemifield. Critically, the auditory cue was always accompanied by a task-irrelevant spatially and temporally coincident visual stimulus. Within several weeks, this caused the animal to orient to the visual cue when it was presented alone. This recovery of visuomotor function was linked to training-induced alterations to inputs from lesion-spared regions of visual association cortex to audiovisual SC orienting neurons (Jiang et al., 2015). Applied in human patients with haemianopia, similar principles of MSI training have been shown to lead to improvements in responses to stimuli in the haemianopic field (Dundon et al., 2015). Recent work suggests that such training effects may be specific to spatially coordinated multisensory training stimuli, and that some neural systems may be more easily trained with AV stimuli than others (Grasso et al., 2016). Based on the sum of these compelling findings, MSI-oriented training in children with ASD seems to offer real promise for accelerating the improvement in MSI function that occurs naturally over the course of typical development. For a schematic of audiovisual MSI development in TD and ASD and the effects of training on this trajectory in ASD, see Fig. 1.

A different approach to remediating MSI function is through closed-loop neurofeedback and/or neurostimulation. Given that atypical neural activity necessarily underlies reduced multisensory processing among individuals with ASD, there is the possibility that this activity can be normalized through appropriate tools. In closed-loop neurofeedback, on-line adaptive changes of an experimental task are made in real time on the basis of neural activity (Sitaram et al., 2017). Indeed, studies indicate that through neurofeedback, an individual can modulate their ongoing neuronal activity, and in turn, the corresponding functions, including attention (deBettencourt et al., 2015), perceptual learning (Shibata et al., 2011), and other forms of learning (for review see Sitaram et al., 2017). A recent study used neurofeedback training in high functioning adolescents with ASD (Datko et al., 2017) to try to selectively increase the motor cortex generated mu rhythm (9–13 Hz). This led to greater activation of sensorimotor areas, as shown in fMRI data collected before and after training. Non-invasive neurostimulation

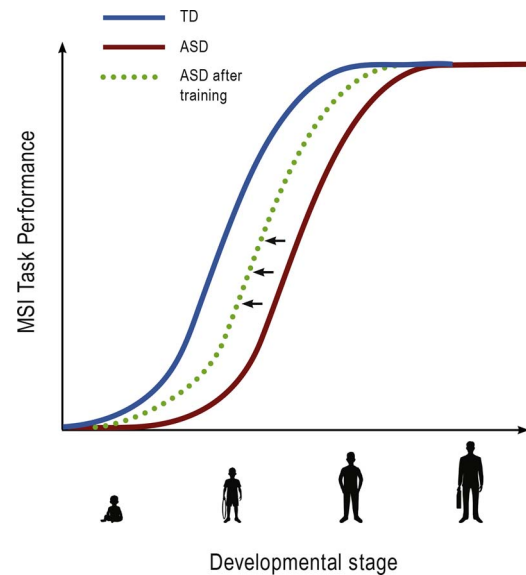


Fig. 1. Developmental delay in Multisensory Integration (MSI) tasks in Autism Spectrum Disorder (ASD). Psychometric developmental curve for MSI performance is altered for individuals with ASD (red curve), compared to individuals with Typical Development (TD; blue curve). While MSI in TD approaches mature levels around adolescence (Brandwein et al., 2011; Gori et al., 2012; Ross et al., 2011), MSI is delayed in individuals with ASD, who usually do not perform comparably to TD before adulthood (Fosse et al., 2015; Irwin et al., 2011; Foss-Feig et al., 2010; Taylor et al., 2010). Behavioral training starting at a young age can potentially shift the amelioration of MSI performance earlier (dashed green curve). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), are also gaining traction for their potential to enhance behavioral and motor training effects and possibly generalize to the processes (e.g., working memory or selective attention) underlying the task being trained (Buch et al., 2017; Looi et al., 2016). The optimal conditions for neuromodulatory stimulation have yet to be established, and there is much ongoing debate regarding the efficacy of the approach (Horvath et al., 2015a,b). Nevertheless, successful implementations in clinical (Brunelin et al., 2012; Brunoni et al., 2013) and healthy (Snowball et al., 2013) populations are reported, and there are well-controlled experiments showing lasting effects that generalize beyond the task explicitly trained on (Looi et al., 2016). To effectively apply biofeedback or neurostimulation to boost MSI in individuals with ASD, recognizing specific rhythmic electrophysiological properties in MSI processes will be critical (Giordano et al., 2017; Goschl et al., 2015; Mercier et al., 2013, 2015; Senkowski et al., 2007).

1.3. Neuro-oscillatory mechanisms and their potential role in MSI impairment

In recent years, significant steps have been made toward understanding the role of neuronal rhythms in perceptual and cognitive processes (Buzsáki et al., 2012; Foxe et al., 1998; Foxe and Snyder, 2011; Schroeder et al., 2010; Singer and Gray, 1995; Thut et al., 2012; Varela et al., 2001). External stimuli can reset the phase of ongoing neuronal oscillations, with phase reset optimizing neural excitability so that sensory areas of the cortex are more receptive when relevant stimuli are expected (Gomez-Ramirez et al., 2011; Lakatos et al., 2008). Furthermore, synchronization between different sensory areas in the cortex is considered to facilitate information transmission (Kaiser et al., 2016; Lakatos et al., 2009; Senkowski et al., 2007), promoting multisensory communication (Mercier et al., 2013) and impacting behavioral outcomes (Fiebelkorn et al., 2011; Mercier et al., 2015). Sensory inputs have been shown to phase-reset on-going neuronal oscillations in low-

level cross-sensory areas (Lakatos et al., 2007; Mercier et al., 2015; Schroeder and Foxe, 2005). For example, auditory stimuli can reset the phase of oscillations in the visual cortex (Fiebelkorn et al., 2011; Lakatos et al., 2009; Mercier et al., 2013; Romei et al., 2012). More generally, cross-sensory inputs reset ongoing cortical activity such that the local response to a region's primary input is enhanced (Foxe and Schroeder, 2005; Lakatos et al., 2007, 2005) and may also serve to trigger inter-regional coherence (Mercier et al., 2015; Sehatpour et al., 2008).

Several groups have suggested that impaired neuro-oscillatory functions may play a significant role in neurodevelopmental and neuropsychiatric disorders, including autism (Brock et al., 2002; Brown et al., 2005; David et al., 2016; Murphy et al., 2014; Simon and Wallace, 2016; Uhlhaas and Singer, 2012). Arguably, even small perturbations in the synchronization of oscillations across cortical areas would lead to deficits in MSI, such as those observed in children with ASD. While there is a dearth of studies examining oscillations in the context of multisensory processing in ASD, evidence of altered oscillatory activity in this population can be found in the unisensory literature. Neural oscillations are usually parsed into the delta (~1.5 to 4 Hz), theta (~4 to 8 Hz), alpha (~8 to 14 Hz), beta (~14 to 30 Hz), and gamma (~30 to 200 Hz) frequency bands. In the context of sensory processing, gamma band perturbations in autism have been, perhaps, most commonly observed. Gamma activity is often associated with the perceptual binding of information (Desmedt and Tomberg, 1994; Gray and Singer, 1989; Tallon-Baudry et al., 1999). Visually-dependent gamma activity was altered in children and adults with ASD in studies using simple visual stimuli (Milne et al., 2009; Snijders et al., 2013), but even more so using complex stimuli such as faces (Grice et al., 2001; Sun et al., 2012), pictures (Buard et al., 2013), and visual illusions (Stroganova et al., 2012). Reduced gamma synchronization was also found for auditory-evoked activity, again using simple stimuli such as pure tones (Edgar et al., 2015; Gandal et al., 2010; Rojas et al., 2008). Gamma band atypicalities are sometimes interpreted as reflecting an excitatory/inhibitory imbalance among inhibitory interneurons, due to disturbance of GABAergic function (Bozzi et al., 2017; Brown et al., 2005; Port et al., 2017; Rubenstein and Merzenich, 2003). Alterations in the generation of alpha-band (8–14 Hz) oscillatory activity have also been observed in ASD and have been associated with altered sensory and attentional functioning. Alpha band activity is often associated with visual processing and attentional processes (Adrian and Matthews, 1934; Foxe and Snyder, 2011; Klimesch et al., 1998), and with the inhibition of task irrelevant sensory information (Foxe et al., 1998; Foxe and Snyder, 2011; Kelly et al., 2009; Worden et al., 2000). Some examples of atypical alpha activity in ASD include the observation of altered phase locking in alpha band to photic stimulation (Lazarev et al., 2009), higher alpha power in ASD to high-spatial frequency stimuli (Milne et al., 2009), and reduced alpha-band attentional suppression mechanisms in the context of visuospatial (Keehn et al., 2017) and intersensory (Murphy et al., 2014) attention tasks. In addition, the sensory-motor mu rhythm (9–13 Hz in humans), which is desynchronized during both the execution and the observation of motor behaviors (Pfurtscheller et al., 2006), does not always modulate in ASD during observed motor action (Bernier et al., 2007; Dumas et al., 2014) but see (Hobson and Bishop, 2017) review for significant methodological concerns regarding the use of this paradigm).

Based on these indications of impaired oscillatory activity in individuals with ASD, a central question is whether impairments in MSI in autism, and specifically integration from distant sensory areas, stem from compromised cross-sensory phase reset or, possibly, from other impaired oscillatory functions in the ASD brain. If the phase of neuronal oscillations indeed plays a critical role in sensory integration, then even a subtle disturbance to the coordination of inter-regional phase relationships might lead to malfunctions in information processing. Fig. 2 conveys this mechanistic model, in which inter regional connections are weaker in the ASD brain, which results in non-synchronous intersensory

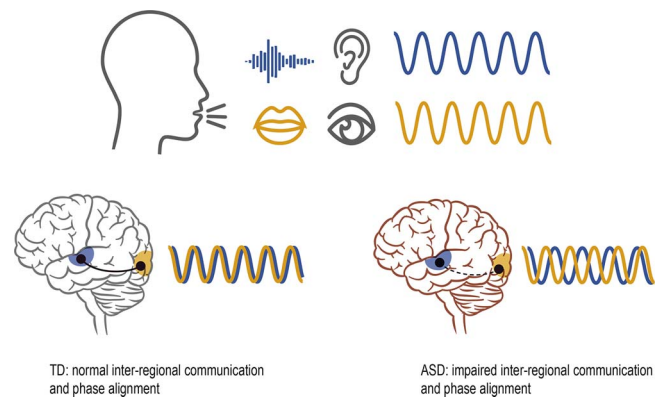


Fig. 2. Proposed model for MSI deficits in ASD. Typical reaction to multisensory stimuli, such as speech, is enhanced due to inter-regional phase alignment of neuro-oscillations (Mercier et al., 2015). Reduced MSI effects in children with ASD is possibly related to reduced interregional communication (Di Martino, 2014; Weng et al., 2010; Long et al., 2016) and, in turn, impaired phase alignment of neuro-oscillations.

activity. Advanced stages of processing such as multisensory integration might be more impacted than basic processing of sensory features. These potential cascading effects would likely have implications for the development of many of the cognitive abilities typically impaired in individuals with ASD. This would of course include communication, which requires coordinated activity across a vast network of cortical regions.

An open question is whether impaired oscillatory processes could be repaired through intervention in ASD. Typically, inter-regional functional connectivity strengthens over development through the maturation of white matter connections and through experience, which parallels gains in cognitive ability (Simmonds et al., 2014). As a result, functional networks become less localized and more distributed, and consequently, connectivity becomes stronger among distant anatomical regions (Fair et al., 2009). In individuals with autism, however, widespread disruptions of white matter microarchitecture have been found in long-range fibers (Koolschijn et al., 2017), which is in line with under-connectivity of long range circuits suggested by functional measures (Assaf et al., 2010; Di Martino et al., 2014; Long et al., 2016; Weng et al., 2010). Reduced connectivity in autism, in turn, could lead to a perturbation in long range signaling, resulting in altered synchronization between the relevant areas. Suboptimal integration would be one result. Based on such a model, resolution of MSI in ASD could be the outcome of increased network connectivity due to naturally occurring developmental changes in connectivity, and/or following interventions such as those described above, and subsequent strengthening of the longer-range pathways.

2. Summary and discussion

Multisensory information that arrives simultaneously to the various sensory organs typically leads to enhancement in processing and behavior. This enhancement is usually promoted by inter-regional communication: synchronized oscillations of cortical activity between different brain regions. While the typical brain develops in a way that facilitates reaction to stimuli through network-level inter-regional communication, this facilitation may well be altered in children and young adolescents with ASD, as seen in a corpus of studies involving stimuli with different degrees of complexity.

Based on several studies that specifically looked at MSI in ASD as a function of development, and based on studies using similar paradigms across different age groups, we see a pattern of amelioration of MSI over age. Children with ASD are usually impaired, showing less effective integration compared to TD. For most tasks, this impairment normalizes by adulthood, with adolescence being the pivotal point. An

exception was seen in a study that involved instantaneous adaptation/calibration, a process that may not be impacted by these developmental gains, and may be related to classic symptoms of autism such as resistance to change and rigidity.

Given the sustained development of MSI seen in ASD, training that is focused on MSI functions, using either behavioral or closed-loop neuromodulatory approaches, holds promise for the early amelioration of MSI in ASD. Critically, this could shift the MSI developmental curve earlier (see Fig. 1) so that MSI is available to impact the emergence of functional skills during critical periods in ASD. The reduced long-range connectivity found in ASD by anatomical and functional imaging studies suggest that one possible mechanism underlying deficits in MSI among individuals with ASD is perturbed cross-sensory oscillatory synchrony. To address this possibility, future studies should directly investigate the degree of synchronization across the neural network under multisensory stimulation conditions. Broader knowledge of how these processes are affected will allow the development of more precise models of the neural mechanisms underlying impaired MSI in autism (Cuppini et al., 2017), and with the appropriate tools, this knowledge may be applied to enhance performance of individuals with autism.

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