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THE NEURODEVELOPMENT OF BASIC SENSORY PROCESSING
AND INTEGRATION IN AUTISM SPECTRUM DISORDER

by

ALICE BROWN BRANDWEIN

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

2014
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Abstract

THE NEURODEVELOPMENT OF BASIC SENSORY PROCESSING AND INTEGRATION IN AUTISM SPECTRUM DISORDER

by

Alice B. Brandwein

Advisors: John J. Foxe, Ph.D. and Sophie Molholm, Ph.D.

This thesis presents three studies that together explore the neurophysiological basis for the sensory processing and integration abnormalities that have been observed in autism spectrum disorder (ASD) since the disorder was first described over half a century ago. In designing these studies we seek to fill a hole that currently exists in the research community’s knowledge of the neurodevelopment of basic multisensory integration -- both in children with autism and as well as in those with typical development. The first study applied event related potentials (ERPs) and behavioral measures of multisensory integration to a large group of healthy participants ranging in age from 7 to 29 years, with the goal of detailing the developmental trajectory of basic audiovisual integration in the brain. Our behavioral results revealed a gradual fine-tuning of multisensory facilitation of reaction time which reached mature levels by about 14 years of age. A similarly protracted period of maturation was seen in the brain processes thought to underlie to multisensory integration. Using the results of this cross-sectional study as a guide, the second study employed a between groups design to assess differences in the neural activity and behavioral facilitation associated with integrating basic audiovisual stimuli in groups of children and adolescents with ASD and typical development (aged 7-16 years). Deficits in basic audiovisual integration were seen at the earliest stages of cortical sensory processing in the ASD
groups. In the concluding study we assessed whether neurophysiological measures of sensory processing and integration predict autistic symptom severity and parent-reported visual/auditory sensitivities. The data revealed that a combination of neural indices of auditory and visual processing and integration were predictive of severity of autistic symptoms in a group of children and adolescents with ASD. A particularly robust relationship was observed between severity of autism and the integrity of basic auditory processing and audiovisual integration. In contrast, our physiological indices did not predict visual/auditory sensitivities as assessed by parent responses on a questionnaire.
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I am fortunate to have had so many wonderful clinical supervisors and professors who have inspired me and developed my skills as a clinician. It is in part because of mentors like Nancy Foldi, Hilary Gomes, Jeffrey Halperin, Juliana Bates, and Natalie Russo that I remain excited and passionate about neuropsychology and child development.

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GENERAL INTRODUCTION

The nervous system's remarkable capacity to combine complementary inputs into unified and meaningful percepts serves to reduce the sensory complexity of the environment and enhance detection, perception, and cognition (Fiebelkorn, Foxe, Butler, & Molholm, 2011; Giard & Peronnet, 1999; Lippert, Logothetis, & Kayser, 2007; Ma, Zhou, Ross, Foxe, & Parra, 2009; Molholm, Ritter, Javitt, & Foxe, 2004; Molholm et al., 2002; Noesselt, Bergmann, Hake, Heinze, & Fendrich, 2008; Ross, L. A., Saint-Amour, Leavitt, Javitt, & Foxe, 2007; Vroomen & de Gelder, 2000). Auditory and visual integration is especially important for processing social and communicative cues, such as speech and emotion recognition (Collignon et al., 2008; Ma et al., 2009; Massaro & Egan, 1996; Ross, L. A., Saint-Amour, Leavitt, Javitt, et al., 2007). The processing of these social and emotional cues is, in turn, a primary area of dysfunction in autism spectrum disorders (ASD); and a focus of both research and treatment. While the notion that individuals with autism process and integrate sensory information differently than others is not new, it has not been adequately explored. Recent research has concentrated on studying higher order cognitive function and complex behaviors, with less attention to the elementary sensory processes that may ultimately contribute to higher order deficits. The goal of this dissertation is to investigate the neurophysiological development of early sensory processing and integration of basic, non-social auditory and visual information. We chose to focus on these early sensory-level processes as we suspect some of the complex social, communication, sensory interests and behaviors characteristic of autism depend in part on the integrity of these fundamental processes and their supporting neural architecture. High-density electrical mapping techniques and established behavioral metrics are used to 1) characterize the neurodevelopmental trajectory of basic audiovisual integration in healthy children (Chapter 1), and 2) assess the integrity of these
fundamental neural processes in ASD (Chapter 2). Drawing on and extending this research, Chapter 3 explores whether neurophysiological and behavioral measures of basic sensory processing and integration are predictive of autism symptom severity and associated sensory sensitivities.

“He used to be afraid of my egg beater, is perfectly petrified of my vacuum cleaner. Elevators are simply a terrifying experience to him. He is afraid of spinning tops.” - Fredrick W., age 6 years; as described by his mother (Kanner, 1943, pp. 222-223)

**Historical perspectives on sensory abnormalities in autism**

As early as 1943, Leo Kanner reported on unusual sensory responses and interests in a group of children whose "outstanding, pathognomonic, fundamental disorder is the children's inability to relate themselves in the ordinary way to people and situations from the beginning of life" (Kanner, 1943, p. 242). In these first published descriptions of autism ¹, Kanner observed that, in addition to showing intense interest in objects (rather than people), unusual language, and repetitive motor behaviors, many of these children displayed an extreme fear of certain noises and had atypical reactions to visual stimuli (e.g., fixating on a small crack in the ceiling). Much of the literature on autism in the decades that followed characterized the autistic child's emotional withdrawal, highlighted the role of parent-child interactions (namely, the concept of the 'refrigerator mother'), and differentiated autism from 'childhood schizophrenia.' However, the idea that sensory systems were somehow abnormal in autism was not completely absent in the early literature (Goldfarb, 1956; Hutt & Hutt, 1965; Hutt, Hutt, Lee, & Ounsted, 1964; Ornitz & Ritvo, 1968a, 1968b), albeit typically discussed within the conceptual framework

¹ Hans Asperger simultaneously described a similar group of children in 1944 (Asperger, 1944)
popular at the time. For example, in the era in which psychodynamic and object relations theories dominated, Goldfarb (1956) wrote that "an alteration in the usual hierarchy of [sensory] receptor preferences and in the relationship of the various sensory modalities" interferes with the child's "understanding of his internal and external worlds," his "empathic responses," and normal communication.

In 1968 Ornitz and Ritvo put forth the idea that the core developmental deficits in autism are caused by a failure to regulate sensory input starting from a very young age (Ornitz & Ritvo, 1968a, 1968b). The authors hypothesized that this pathological process has a neurophysiological basis, namely that there is a disruption of the equilibrium of nervous system's excitatory and inhibitory activity. This idea is remarkably similar to the contemporary view that neurophysiological dysfunction contributes to aberrant social, perceptual, and cognitive development. But Ornitz's and Ritvo's ideas did not gain much traction, perhaps because they were not supported by direct empirical evidence.

Hutt and colleagues (1965) were among the first to systematically observe the responses of a (small) group of autistic children as they encountered varying levels of sensory stimulation. They found that the children's peculiar behaviors (e.g., stereotypies, reduced exploratory behavior) increased when they were exposed to more complex sensory environments. The authors theorized that children with autism operated at a chronically high level of arousal and that the increased sensory inputs raised their arousal level further (Hutt & Hutt, 1965; Hutt et al., 1964). In this view, the abnormal responses to sensory bombardment were conceived of as a defense mechanism to protect the child from over-arousal by blocking further sensory input. The authors suggested that EEG records showing desynchronized activity was evidence that their autistic subjects were in a chronically high level of arousal (Hutt & Hutt, 1965). Unfortunately
Hutt and Hutt’s conclusions were based on data from only six autistic subjects (and no control group) making their theory difficult to evaluate.

As the field of experimental psychology evolved, a handful of studies examining sensory processing in autism emerged. This body of research was primarily concerned with psychophysical aspects of sensation and perception, particularly sensory dominance and visual discrimination. Hermelin and O'Conner (1970) summarized a number of studies including a series of experiments from their research group, and concluded that autistic children, like controls, showed visual (over auditory) dominance. They concluded that overall visual abilities were similar in autistic and non-autistic children but that the children with autism showed deficits in sustained visual attention, a finding that highlights the need to take visual attention into account when assessing this population. Such studies were significant in that they constituted some of the first applications of experimental methodology to the study of children with autism; however, there were few attempts to integrate findings and translate them into the clinical realm.

At the same time as experimental psychologists were employing a data-driven approach to study psychophysical responses in autism, clinicians were developing theories and therapies based on their clinical observations. A. Jean Ayres’, a renowned occupational therapist and researcher, pioneered sensory integration therapy for the treatment of certain learning and behavioral disorders. She defined sensory integration as “the neurological process that organizes sensations from one’s own body and from the environment and makes it possible to use the body effectively in the environment” (Ayres, 1979, p. 11). Though Ayres’s theories of sensory integration and dysfunction were not originally put forth as explanations for autism symptomology specifically, they quickly became associated with the disorder. Sensory
integration therapy (sometimes referred to as a ‘sensory integrative approach’), which is an individually-tailored and child centered intervention based on principles from Ayres’s theory, took off in the 1970s and continues to be a popular component of treatment for autism (Rogers & Ozonoff, 2005). Sensory-based therapies include playful, yet challenging activities in a sensory rich environment that is continuously adapted to meet the child's new abilities (Schaaf & Miller, 2005). For example, an occupational therapist might have a child rotate on a swing while throwing a beanbag at different targets and listening to therapeutic music on headphones to improve the child's ability to integrate the vestibular, visual, and auditory senses.

At the turn of the century there was a shift toward more cognitive-perceptual explanations of psychopathology. Reflecting this, theories of autism tended to focus on what is often referred to as the ‘cognitive phenotype’ of ASD. This so-called cognitive style, which includes perseverance, rigidity, uneven intellectual abilities, and a tendency to be detail oriented (e.g., Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Tager-Flusberg & Joseph, 2003) took center stage in many of the popular theories that emerged in the 1990s. The notion that the integration of sensory inputs is faulty in autism is incorporated into many of these theories. For example, the premise of the ‘weak central coherence’ theory is that the perceptual and cognitive atypicalities observed in ASD are related to a decreased ability to integrate information into a context that allows one to construct higher-level meanings and representations (Frith, 1989; Frith & Happe, 1994). Features of stimuli are processed in a piecemeal manner with a bias towards 'local' rather than 'global' processing, and as a result individuals do not readily perceive or recognize the overall gestalt. A variant of the 'weak central coherence' account is the 'enhanced perceptual functioning' model of autism which postulates that the bias towards 'local' processing is a result of enhanced low-level perceptual operations, not of a deficit of global processing and
feature integration (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006; Plaisted, Saksida, Alcantara, & Weisblatt, 2003). Minshew and colleagues (1996; 1997) proposed that the underlying deficit in ASD is one of ‘complex information processing’, and emphasized that impaired abilities were those that placed high demands on information processing and integration. According to this theory, simple processing at the perceptual level is intact (or enhanced) but cognitive processing at 'higher' brain levels is abnormal. Similar to the 'complex information processing' theory, is the 'executive dysfunction' theory which proposes that impaired executive functioning (the umbrella term for a wide range of processes such as planning, flexibility, impulse control, problem solving, and initiation) is a primary deficit in autism (McEvoy, Rogers, & Pennington, 1993; Ozonoff, Pennington, & Rogers, 1991; Ozonoff, Strayer, McMahon, & Filloux, 1994). Impaired executive functioning, which is associated with frontal lobe abnormalities, is offered as an explanation for problematic behaviors including perseveration, rigidity, and decreased initiation of new responses.

‘Weak central coherence,’ ‘enhanced perceptual functioning,’ ‘complex information processing,’ and ‘executive dysfunction’ theories are appealing in that they have the potential to explain a large number of the symptoms observed in ASD, and empirical findings from studies examining perceptual and cognitive functioning can often be interpreted in terms of these general models. On the other hand, a significant limitation of these theories is that they are neurally unspecific and basically not falsifiable from a physiological or anatomical standpoint. These theories typically make reference to and hypothesize a role for neural involvement, but they are designed around cognitive constructs for which the underlying neural circuitry is largely unknown. For example, even the 'executive dysfunction' theory of autism, which implicates frontal abnormalities, is based primarily on findings from neuropsychological and behavioral
The few neuroimaging studies of individuals with autism performing executive function tasks showed widespread brain abnormalities rather than a deficit localized to frontal brain regions (e.g., Gilbert, Bird, Brindley, Frith, & Burgess, 2008; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Kleinhans, Schweinsburg, Cohen, Muller, & Courchesne, 2007; Schmitz et al., 2006; Velazquez et al., 2009).

The purpose of the current set of investigations is not to discriminate between the different neurocognitive models of ASD, but rather to focus in on very specific and crucial processes (basic sensory processing and integration) which can be measured both neurophysiologically and behaviorally. By assessing these processes at the neurophysiological level, these studies have the potential to increase our insight into the brain mechanisms that underlie the ASD phenotype.

"The baby, assailed by eyes, ears, nose, skin, and entrails at once, feels it all as one great blooming, buzzing confusion; and to the very end of life, our location of all things in one space is due to the fact that the original extents or bignesses of all the sensations which came to our notice at once, coalesced together into one and the same space. There is no other reason than this why "the hand I touch and see coincides spatially with the hand I immediately feel."

- William James in The Principles of Psychology (1890, p. 488)

**The development of early sensory processing and integration**

Before we can begin to assess the integrity of basic multisensory processes in autism, it is critical to have an understanding of basic sensory processing in typical development. In terms of their basic neural architecture, the auditory and visual systems that support unisensory
processing are relatively well-developed at birth. For example, brainstem responses confirm that sound detection is present as early as 28 weeks gestation (Starr, Amlie, Martin, & Sanders, 1977), and that auditory intensity discrimination is well-developed by 6 months of age (Anslin & Hunt, 2001). Compared to audition, vision is less mature at birth. Contrast sensitivity and spatial vision are poor in the newborn (Dannemiller, 2001; Maurer & Lewis, 2001). Visual acuity, motion tracking, spatial vision, depth perception and color vision improve rapidly over the first six months (Dobson & Teller, 1978; Maurer & Lewis, 2001) but many functions do not reach adult-like levels until early-mid childhood (e.g., Leat, 2009). While the basic elements of unisensory processing seem to be in place early on, it is known that experience can impact both lower level and higher order cortical anatomy and physiology (Gaser & Schlaug, 2003; Tervaniemi, Just, Koelsch, Widmann, & Schroger, 2005; Zhang, Kuhl, Imada, Kotani, & Tohkura, 2005). In other words, the nervous system's ability to interpret auditory and visual stimuli is a continuous and dynamic process that develops over the lifespan, but the fundamental sensory components of unisensory processing are relatively well-established in infancy. We have yet to discover whether or not this is the case for basic multisensory processes.

According to Piaget, the infant’s senses are initially separate and become coordinated through experience (as described in Butterworth, 1988). While Piaget's theories were based solely on behavioral observations, neurophysiological studies provide support for his ideas. Animal research, for example, has allowed us to explore the development of the brain's ability to integrate multisensory inputs. Findings from research on cat neonates indicate that the neural processes that underlie basic multisensory integration (MSI) are immature at birth and depend to a large extent on the sensory experiences of the animal (Wallace, Carriere, Perrault, Vaughan, & Stein, 2006; Wallace, Perrault, Hairston, & Stein, 2004; Wallace & Stein, 1997). In these series
of experiments Wallace, Stein and colleagues elegantly showed that in kittens, the subcortical 'multisensory neurons' (which, in mature cats responded to auditory, visual, and somatosensory stimuli) initially responded only to inputs from one sensory modality. The integrative properties of these neurons emerged over the course of several months and were highly impacted by the early experiences on the animal.

For ethical reasons, human infant research on multisensory processing is largely restricted to behavioral studies. A number of preferential looking studies demonstrated that the ability to detect, learn, and remember audiovisual relationships (such as face-voice pairings, temporal correspondence) is present in infancy (Bahrick, Hernandez-Reif, & Flom, 2005; Kuhl & Meltzoff, 1982; Lewkowicz, D. J., 1992; Patterson & Werker, 2003). However, emerging research indicates that the capacity to use multisensory cues optimally to enhance performance improves gradually over development (Bair, Kiemel, Jeka, & Clark, 2007; Barutchu et al., 2010; Gori, Del Viva, Sandini, & Burr, 2008; Neil, Chee-Ruiter, Scheier, Lewkowicz, & Shimojo, 2006; Ross, L. A. et al., 2011). For example, Neil and colleagues (2006) demonstrated that multisensory facilitation of spatial localization is not present at birth and does not emerge until late infancy. Though present, audiovisual integration, as measured by non-linear multisensory facilitation of reaction time, was still immature in 10 month old infants. A major limitation of this study is that it only considered infants from 2-10 months old and adults. Under this limitation, the full developmental trajectory of MSI was not characterized. Subsequent behavioral studies indicated that the optimal integration of auditory and visual inputs for functional purposes (e.g., improvements in behavior such as speeding up of reaction time, accuracy of response, enhanced speech recognition, etc.) continues to improve across childhood and even into adolescence (Barutchu, Crewther, & Crewther, 2009; Barutchu et al., 2010; Ross,
These behavioral findings, together with evidence from single cell recordings in animals (e.g., Wallace et al., 2006; Wallace, Perrault, et al., 2004; Wallace & Stein, 1997), support the view that multisensory enhancement of behavior increases with post-natal brain maturation and that it is dependent on experience. Because the vast majority of neurophysiological research on basic MSI has been limited to adults and non-human species, little is known about the human child's capacity to integrate basic auditory and visual information at the neural level. Assaying MSI using both behavioral and neurophysiological measures across a large age range will help fill this gap in our knowledge and will provide us with a starting point to examine MSI in children with ASD.

"I love long, long car rides...The car motion and the visual scenery flashing by it allow you to block out all other sensory input and focus on one." - Carly Fleischmann, a teenager with 'extreme' autism (2012).

**Empirical research on MSI and autism**

While 'multisensory integration' (MSI) means different things to different research groups, here we consider MSI as a process which indicates that two or more sensory systems interact; that is, at neurophysiological level. Often the neurophysiological basis of MSI cannot be ascertained directly from purely behavioral findings, but in general we consider a behavior to reflect MSI when there is evidence that one sensory input affected the other at an early stage of processing. In other words, if an individual's response to a multisensory stimulus is different (faster reaction time, novel percept) from its constituent unisensory stimuli, multisensory integration is often assumed to be involved (Stein et al., 2010). There are a number of other
frequently studied multisensory processes, such as cross-modal matching and temporal discrimination, which depend on the association, but not necessarily the integration, of sensory inputs. Though this dissertation discusses studies looking at multisensory processing because this is where the bulk of developmental research is concentrated, our focus is on MSI as it has the capacity to tell us of the underlying neural processes at work.

**MSI of social stimuli.** Despite the long-standing perspective that integrative processes are impaired in ASD, empirical research on the topic is relatively sparse; with the majority of studies focused on how individuals with ASD integrate socially complex audiovisual stimuli such as faces and speech sounds. The most common method for examining audiovisual speech perception is the 'McGurk' illusion. In a classic McGurk paradigm, participants are presented with incongruent visual and auditory speech stimuli (e.g., a video of a person articulating 'ga-ga' dubbed onto the sound 'ba-ba'). Individuals often report that they hear an illusory fused sound (e.g., 'da-da') that is different from both the auditory and visual input (McGurk & MacDonald, 1976) or hear the visually presented phoneme pair reflecting the influence of visual inputs on auditory speech perception (Saint-Amour, De Sanctis, Molholm, Ritter, & Foxe, 2007). The robust and reliable McGurk illusion (which also occurs to a lesser extent for non-speech sounds; e.g., Saldana & Rosenblum, 1993) is considered a powerful tool for assaying the integrity of audiovisual speech perception, and it highlights the influence of visual input on auditory speech perception.

Studies of the McGurk effect in ASD generally demonstrate that children with ASD are less susceptible to this illusion than their typically developing peers (de Gelder, Vroomen, & van der Heide, 1991; Irwin, Tornatore, Brancazio, & Whalen, 2011; Mongillo et al., 2008). Findings from a recent study showed that nine month-old infants at risk for ASD displayed unusual
looking patterns towards McGurk-like stimuli (Guiraud et al., 2012). Though there are significant methodological limitations to this study, particularly its use of a preferential looking paradigm to index AV (audiovisual) integration (an issue discussed in subsequent sections), Guiraud and colleagues’ finding that high-risk infants demonstrated usual looking patterns to AV speech is notable.

Audiovisual speech perception can also be assayed using 'speech in noise' paradigms wherein individuals are presented with audiovisual speech in varying levels of background noise (e.g., Ross, L. A., Saint-Amour, Leavitt, Javitt, et al., 2007). Since in the real world speech is often heard in the presence of background noise, ‘speech in noise’ paradigms have significant ecological validity. In ASD this benefit is reduced; that is, when children with ASD are presented with audiovisual speech embedded in noise, they show less benefit from the addition of visual information than do controls (Foxe et al., 2013; Irwin et al., 2011).

Findings from 'speech and noise' and 'McGurk' studies are fairly consistent in showing that individuals, or at least children, with ASD benefit less from the visual component of audiovisual speech; but factors other than the actual integration of auditory and visual inputs may be at work. For example, lip reading tends to be poorer in individuals with ASD (Foxe et al., 2013; Iarocci, Rombough, Yager, Weeks, & Chua, 2010; Irwin et al., 2011; Smith & Bennetto, 2007; Taylor, Isaac, & Milne, 2010; Williams, J. H., Massaro, Peel, Bosseler, & Suddendorf, 2004), and some researchers have shown that atypical audiovisual speech perception can be at least partially attributed to reduced lip reading ability (Iarocci et al., 2010; Irwin et al., 2011; Smith & Bennetto, 2007; Williams, J. H. et al., 2004). Poor lip reading ability could indicate a visual (unisensory) or higher-level (language) processing deficit, either of which could interfere with MSI. However, data from Foxe and colleagues (Foxe et al., 2013) strongly suggest that
poor performance by children with ASD on an audiovisual speech perception tasks reflects a true
deficit in integrating the audio and visual signals, independent of any difficulties that may exist
in processing unisensory stimuli and/or attending to other more perceptual aspects of the stimuli.
It is also worth considering that poor lip-reading might actually be a corollary of abnormal
audiovisual integration since the ability to read lips arises though learning about associations
between auditory and visual information.

**MSI of non-social stimuli.** To better understand whether individuals with ASD have
impairments in MSI independent of their known deficits in processing socially-laden stimuli, it is
necessary to examine how this population integrates basic, non-social stimuli. Recognizing this
issue, Mongillo and colleagues (2008) employed tasks using non-social stimuli (bouncing balls)
in addition to tasks with social stimuli (human faces and voices, McGurk-type paradigms) to
characterize the nature of audiovisual processing in school-age children and adolescents with
ASD. For the non-social stimuli the authors presented congruent and incongruent audiovisual
pairings of bouncing balls. The moving image of a bouncing ball was paired either with the
sound of the same ball bouncing (congruent), or with the sound made by a ball of a different size
or composition (incongruent). Children with ASD correctly identified ‘matched’ and
‘mismatched’ pairs of bouncing balls similarly to age and IQ-matched children without ASD. In
contrast, the same group of children with ASD performed more poorly than the control group on
three of the four tasks involving human faces and voices. Although the authors' hypothesis that
children with ASD have more pronounced difficulties processing AV human stimuli than AV
object (non-social) stimuli is largely supported, the degree to which these findings reflect intact
MSI of non-social information is questionable due to the nature of the tasks. In addition, AV
matching tasks in general do not provide sufficient evidence that MSI has occurred, an issue that is addressed in subsequent sections.

Findings that children with ASD perform similarly to those with typical development on perceptual tasks that use non-social audiovisual stimuli (e.g., Bebko, Weiss, Demark, & Gomez, 2006; Mongillo et al., 2008) are encouraging in that they suggest that a form of audiovisual processing occurs on some level. However, studies that measure preferential looking and matching behaviors are significantly limited in the extent to which they can inform us about sensory integration. Arguably the most important issue is that it is virtually impossible to determine at what stage of processing the audio and visual inputs are associated. This is not an insignificant issue, as the earliest 'sensory' stages of processing are relatively automatic, while later stages of information processing reflect more complex perceptual and dynamic cognitive states that are likely shaped by experience and influenced by a number of variables (discussed in subsequent sections). Preferential looking towards one set of stimuli over another (e.g., AV speech stimuli, as in Guiraud et al., 2012) may be related to novelty, familiarity, and affective salience of the stimulus set rather than its fundamental multisensory properties.

An additional issue with applying preferential looking and stimulus matching paradigms (e.g., Bebko et al., 2006; Guiraud et al., 2012; Mongillo et al., 2008; Vaillant-Molina & Bahrick, 2011) to the study of MSI is that such tasks do not sufficiently measure whether or not the stimuli are integrated. Accuracy on matching tasks requires only that the individual perceives two stimuli as emanating from the same event, and not necessarily that he or she integrates or combines the inputs at the sensory level. For example, it is possible to recognize that an audio soundtrack is out of sync with a visual display (as in Bebko et al., 2006) or that the sound and video of a bouncing ball do not match (e.g. Mongillo et al., 2008) at a post-perceptual stage of
processing; that is, after the unisensory inputs are processed separately. To better assess whether or not a behavior or neural signal is the result of MSI or of direct interactions between the brain’s unisensory systems, it is necessary to show that the response to the multisensory event is somehow different (e.g., statistically faster, more robust, of a different size) from the best unisensory response (Stein et al., 2010).

"If someone was to see the world through my lens. It'd be a confusing place.... I am constantly aware of electricity humming, when I walk into a shop I'm hit with sound and light cauterizing my senses and leaving me with a feeling not unlike concussion."

- Elliot Cooper, a young adult with autism (Cooper).

**Neurophysiological approaches to studying sensory processes and integration**

One of the most significant barriers to drawing meaningful conclusions from investigations of sensory processing in ASD is the numerous definitions and conceptualizations of 'sensory processing'. In much of research, sensory processing is defined by what can be measured, and what is measured is often dictated by the perspective and expertise of the observer. For example, parents of children with ASDs may use the term 'sensory processing' to describe their child’s unusual sensory responses to naturally occurring stimuli in their environment. Therefore parent report measures of sensory processing, of which the most widely used are the Sensory Profile (Dunn, W., 1999) and the Short Sensory Profile (McIntosh, Miller, Shyu, & Dunn, 1999), include items concerning the child’s response to sounds (e.g., background noise, loud and unexpected noise, calling the child’s name), to visual stimuli (e.g., bright light), to touch (e.g., fabric against skin, hugs), and to foods and smells. Under the heading of sensory
processing, parent questionnaires also consider behaviors such as intense looking at objects/people, seeking movement (spinning, rocking), excessive touching of people/objects, and strong preferences for certain tastes/smells. Most sensory processing questionnaires were developed by occupational therapists with the goal of clustering behaviors that are conceptualized as sensory-based (such as the items described above) into subtypes of sensory dysfunction (for example, the Sensory Profile describes sensation seeking, sensitivity to stimuli, sensation avoiding and poor registration). Cognitive psychologists on the other hand tend to discuss sensory processing in the context of attention (e.g., abnormal orienting to stimuli, unusual attention to parts rather than wholes, local versus global processing, attention to non-social rather than social/linguistic stimuli). From a more neurophysiological perspective, sensory processing is thought of as the nervous system’s response (e.g., neural transmission, cortical activation, psychophysical reactions) to sensory input from the external environment. A major benefit of neurophysiological research is that the dependent measure is the neural response itself, thus there is an opportunity to elucidate the underlying neuropathology directly from the source rather than indirectly through cognitive constructs and subjective reports.

A significant shortcoming of purely behavioral research is that the neural circuitry that contributes to the behavior in question cannot be ascertained. That is, different neural processes may underlie the same behavioral response patterns. One may question why it matters exactly how the brain integrates inputs if the behavioral endpoint is the same. The answer lies in understanding whether individuals with autism integrate inputs optimally and efficiently. Consider the simple analogy of two cars taking different routes to the same routine/familiar destination: though they both arrive at the same destination, their experiences along the way could be different, which could have consequences ‘down the road’ (so to speak). For example,
one car may have used more gas, put additional wear and tear on the brakes, paid unnecessary tolls, etc., leaving that car less prepared to go to its next destination. The small amount of behavioral research that exists suggests that individuals with ASD combine basic auditory and visual inputs at some level (Bebko et al., 2006; Foss-Feig et al., 2010; Mongillo et al., 2008; van der Smagt, van Engeland, & Kemner, 2007); i.e., they make it to the first destination. However, if the neural route that led to this point of 'integration' is suboptimal, there may be downstream consequences for higher-order processes (i.e., the next destination) such as those involving more complex and/or socially relevant stimuli, more difficult and effortful tasks, etc. This analogy is not in any way meant to suggest that MSI is a simple linear process with one step determining the next, but instead to highlight the importance of using techniques that assess how the brain integrates multisensory inputs rather than relying solely on behavioral observations.

**Neurophysiological techniques.** The high temporal millisecond resolution of neurophysiological techniques makes them an ideal methodology to answer questions about the rapidly occurring sensory and perceptual processes that underlie cognition and behavior. Another advantage of electrophysiological methods is that they provide information about stimulus processing without requiring a behavioral response (Luck, 2005) which is valuable when collecting data from individuals who cannot or will not provide a behavioral response (individuals who are low-functioning, very young, or motor-impaired) or when interested in measuring brain responses during passive tasks. Single cell, intracortical, and intracranial recordings have provided the field valuable information about how the brain deals with multisensory inputs. For example, Stein and Meredith's seminal and extensive investigations of multisensory neurons in the superior colliculus established a set of governing principles of MSI at the cellular level (see Stein, BE & Meredith, 1990; Stein, B. E. & Meredith, 1993).
Recording electrical activity at the scalp, using extracranial electrodes, provides data similar to recordings that penetrate the skull and brain, but it has the advantage of being completely non-invasive, ethically acceptable, and well-tolerated by pediatric and clinical populations. Scalp electrodes measure the summation of synchronous neural activity, from hundreds of different neural sources, volume conducted to the scalp. The ongoing electrical brain activity recorded from the scalp is called electroencephalography (EEG). The brain’s response to a single stimulus or event is not readily visible in an EEG because it is embedded in the simultaneously occurring ongoing brain activity. To extract the ‘signal’ (the brain’s response to a specific event) from the ‘noise’ (the thousands of ongoing brain processes), many trials of the given stimulus are presented and the EEG tracings from all of the stimulus presentations are averaged together. In the averaging process, brain activity that is not time-locked is averaged out. The waveform that emerges, an event related potential (ERP), represents the brain’s response, time-locked to a specific stimulus or event. ERPs are comprised of sequences of negative and positive peaks, often referred to as components, which reflect the flow of information in the brain (Luck, 2005). The ERP components most relevant to the questions posed in this thesis are the sensory components which appear rapidly after stimulus presentation and are most sensitive to the basic physical properties of the stimulus. These obligatory ERPs are relatively automatic and reflect the elementary pre-perceptual processes which are the focus of the current investigations.

**Models of MSI.** Up until the late 1990s, the standard assumption about how multisensory stimuli were processed in the brain was that information coming through different sensory systems projected to their respective unisensory cortices (e.g., auditory inputs projected to primary auditory cortex, and visual inputs to primary visual cortex). This hierarchical view of
sensory processing maintained that unisensory inputs underwent extensive, multistage processing within their unisensory pathways before the two sets of signals converged in multisensory cortical regions associated with higher-order stages of processing (e.g., so-called association areas and frontal regions). Imaging evidence showing MSI in supposedly 'sensory specific' regions was generally attributed to feedback connections from the later stage multisensory regions (e.g., Calvert et al., 1999). Feedback activation of primary sensory areas is certainly part of the picture, but, in the last decade, findings from neurophysiological and anatomical studies offers an expanded view of MSI -- one that suggests that integration occurs early in processing through lateral and feed-forward connections.

Giard and Peronnet (1999) and Molholm and colleagues (2002) were among the first to report early neural interactions between auditory and visual inputs in humans using ERPs. Both studies, one using an object recognition task (Giard & Peronnet, 1999), and the other a simple reaction time task (Molholm et al., 2002), revealed audiovisual interactions over occipital scalp between 40-50 ms after stimulus presentation, which is in the time frame of the earliest inputs into visual cortex. The early timing and topography of these effects raised the possibility that the interactions were generated in lower level visual cortex rather than in higher order cortical areas. The remarkable discovery of direct monosynaptic connections between primary auditory and visual cortices (Falchier, Clavagnier, Barone, & Kennedy, 2002; Rockland & Ojima, 2003) provides a potential anatomic substrate for what appears to be early, low-level multisensory interactions in primary sensory cortices. Collectively, neurophysiological and anatomical data support a model of cortical MSI that can begin during the initial phase of sensory processing, within cortical regions traditionally written off as purely unisensory. While progress has been made in elucidating the spatiotemporal properties of cortical MSI in the mature brain, how and
when these processes come on line in the developing brain, and whether or not these processes are disordered in autism, remains an enigma.

**Proposed studies and goals**

This thesis presents three studies that together explore the neurophysiological basis for the sensory processing and integration abnormalities that have been observed in autism since the disorder was first described over half a century ago. In designing these studies we seek to fill a hole that currently exists in the research community’s knowledge of the neurodevelopment of basic MSI -- both in children with autism and as well as in those with typical development. Having a clearer understanding of what basic audiovisual integration looks like at the neural level in healthy children, a neglected population in this research area, is an important first step in assessing the integrity of these processes in children with autism.  **Chapter 1**, the first study, applies well-defined ERP and behavioral measures of MSI (as used previously to assess MSI in healthy adults; Molholm et al., 2002) to a large group of healthy participants ranging in age from 7 to 29 years, with the goal of detailing the developmental trajectory of basic audiovisual integration in the brain. Using the results of this cross-sectional study as a guide, **Chapter 2**, the second study, employs a between groups design to assess differences in the neural activity and behavioral facilitation associated with integrating basic audiovisual stimuli in groups of children with ASD and TD (aged 7-16 years).  **Chapter 3**, the concluding study, assesses whether neurophysiological measures of sensory processing and integration predict autistic symptom severity and parent-reported audiovisual sensory sensitivities. This is a compelling question, because findings may lead to the future development of biological markers which have the potential to aid in early identification of ASD and may ultimately guide clinicians in the development of more individualized and effective interventions.
CHAPTER 1
The Development of Audiovisual Multisensory Integration Across Childhood and Early Adolescence: A High-Density Electrical Mapping Study

Abstract

The integration of multisensory information is essential to forming meaningful representations of the environment. Adults benefit from related multisensory stimuli but the extent to which the ability to optimally integrate multisensory inputs for functional purposes is present in children has not been extensively examined. Using a cross-sectional approach, high-density electrical mapping of event-related potentials (ERPs) was combined with behavioral measures to characterize neurodevelopmental changes in basic audiovisual (AV) integration from middle childhood through early adulthood. The data indicated a gradual fine-tuning of multisensory facilitation of performance on an AV simple reaction time task (as indexed by race model violation), which reaches mature levels by about 14 years of age. They also revealed a systematic relationship between age and the brain processes underlying multisensory integration (MSI) in the time frame of the auditory N1 ERP component (~120 ms). A significant positive correlation between behavioral and neurophysiological measures of MSI suggested that the underlying brain processes contributed to the fine-tuning of multisensory facilitation of behavior that was observed over middle childhood. These findings are consistent with protracted plasticity in a dynamic system and provide a starting point from which future studies can begin to examine the developmental course of multisensory processing in clinical populations.
Introduction

The ability to construct meaningful internal representations of the environment depends on integrating and segregating the myriad multisensory inputs that enter the nervous system at a given moment. Not surprisingly, it has been firmly established that as adults we frequently benefit from multisensory inputs when they represent redundant or complementary features of objects and events. For example, we react more quickly to the presence of multisensory compared to unisensory objects, and we are often better able to identify an object or event when it is conveyed through more than one sensory modality (Forster, Cavina-Pratesi, Aglioti, & Berlucchi, 2002; Gondan, Niederhaus, Rösler, & Röder, 2005; Lovelace, Stein, & Wallace, 2003; Molholm et al., 2002; Ross, L. A., Saint-Amour, Leavitt, Javitt, et al., 2007; Ross, L. A., Saint-Amour, Leavitt, Molholm, et al., 2007). As might be expected, children too benefit from related multisensory inputs (Barutchu et al., 2010; Gori et al., 2008; Neil et al., 2006). A number of behavioral studies show that infants are capable of recognizing relationships among multisensory inputs (Bahrick et al., 2005; e.g., Kohl & Meltzoff, 1982), suggesting that from very early in development, multisensory associations are formed and temporal relationships between multisensory inputs recognized. For example, using a preferential looking paradigm, Patterson and Werker (2003) showed that 2 month old infants were able to match vowel information in faces and voices, suggesting that by 2 months of age, if not earlier (2 months was the youngest age these authors tested due to issues of reliability and visual acuity in younger infants), some form of multisensory association occurs. Similarly, Lewkowicz (1992) found that when presented with an audiovisual compound stimulus (a bouncing object on a video screen), infants in all age-groups tested (4-, 6-, 8-, and 10-month olds), were sensitive to the temporal relationships between auditory and visual stimuli. Notably, infant behavioral studies on
multisensory processing for the most part test whether the infants have noted relationships between presumably distinct stimulus representations, whereas they do not measure whether the multisensory inputs have been integrated (see Stein et al., 2010 for discussion of this issue). Studies in later childhood (usually with children 6 and older), where multisensory influences on perception can be more reliably assayed, demonstrate the influence of multisensory information on size judgments (Gori et al., 2008), speech percepts (Barutchu et al., 2010), and balance (Bair et al., 2007).

Still, optimal benefit from multisensory inputs often requires experience, and there is every reason to expect that there is a typical developmental course for the “tuning-up” of multisensory integration (Bair et al., 2007; Lewkowicz, D. J. & Ghazanfar, 2009; Lewkowicz, D. L., 2002). Bair and colleagues (2007) showed that the ability to optimally use visual and somatosensory multisensory cues to maintain balance improves between the ages of 4 and 10 years, and preliminary data from our laboratory suggest that the capacity to benefit from visual inputs to understand auditory speech presented in a noisy environment improves dramatically as a function of age (Ross, L.A. et al., 2008). These latter data show that the fine-tuning of optimal multisensory integration continues throughout childhood and probably even into adolescence. Thus, it is clear from infant studies that the ability to associate stimuli from separate sensory modalities emerges very early on, and from studies of later childhood that the integration of these inputs for functional purposes changes dramatically over the course of development, and in some cases even extends from the middle years into adolescence.

To date, knowledge of the development of the neurophysiological processes that underlie multisensory integration (MSI) comes largely from animal studies. For the most part these have focused on the post-natal emergence of multisensory neurons, and on the effects of dramatic
manipulations of the multisensory environment on the development of these neurons. For example, neurophysiological studies in cats indicate that subcortical and cortical multisensory neurons are initially responsive to only one type of sensory input (i.e., they are unisensory neurons), with responsivity to more than one type of sensory input emerging over the course of early development, and integrative properties emerging yet later than simple co-registration (Stein, B. E., Labos, & Kruger, 1973; Wallace et al., 2006; Wallace, Perrault, et al., 2004; Wallace & Stein, 1997). Further it has been found that altering the sensory environment can dramatically affect the receptive fields of multisensory neurons (Carriere et al., 2007). In a most compelling demonstration, auditory and visual stimuli were only ever presented together in a systematically misaligned configuration. In this case, multisensory neurons in the superior colliculus were found to co-register the spatially misaligned auditory and visual stimuli. In contrast, they did not show typical co-registration of the stimuli when they were presented in a spatially aligned configuration (Wallace & Stein, 2007). Thus, there is a huge degree of plasticity in the receptive fields of multisensory neurons that maps over development.

One approach to behaviorally assessing whether MSI has occurred is to compare reaction times to unisensory stimuli to reaction times to multisensory stimuli. When behavioral facilitation for the multisensory condition is shown, a test is performed to determine whether this “speeding up” exceeds the amount of facilitation predicted by the statistical summation of the fastest unisensory responses (Miller, J., 1982; Miller, J. O., 1986). When this statistical threshold is exceeded and hence the so-called “race model” is violated, it can be concluded that MSI has occurred. Numerous studies with adults have used this approach and demonstrated MSI for stimuli containing “redundant” bisensory targets (e.g., Harrington & Peck, 1998; Hughes, Reuter-Lorenz, Nozawa, & Fendrich, 1994; Maravita, Bolognini, Bricolo, Marzi, & Savazzi,
Only a few studies have similarly evaluated MSI in children. One failed to reveal a clear developmental trajectory in children from 6 to 11 years of age (Barutchu et al., 2009). Whereas another study of audiovisual integration, during the first year of life, found that while infants of all ages had faster reaction times to audiovisual stimuli compared to the unisensory stimuli, only the oldest infants (those 8-10 months old) exhibited reaction times faster than those that would be predicted by simple statistical summation (Neil et al., 2006). However unlike typical reaction time paradigms in adults which require an intentional motor response, these measures were taken from infants and were accordingly constrained to associated stimulus-reactive head or eye movements, the timing of which were measured on the order of seconds rather than milliseconds. Accordingly these intriguing findings must be interpreted with caution.

In the face of a considerable body of work investigating the neurophysiology of MSI in human adults and in animals, there is a marked dearth of corresponding work on the development of MSI in humans. The aim of the present study was to examine the developmental trajectory of audiovisual integration in typically developing children from the ages of 7 to 16 years, and in adults, using both behavioral and neurophysiological methods. The technique of high-density electrical mapping was used to measure the temporal and spatial dynamics of basic MSI while participants performed a simple reaction time task to auditory and visual stimuli presented simultaneously or alone (Molholm et al., 2002, 2006). Based on findings from both behavioral research in human infants, and neurophysiological research in animals, it was expected that by 7-9 years of age, the youngest age-group considered, electrophysiological measures would reveal a complex pattern of MSI. It was also expected that the precise timing and scalp topography of multisensory processing would not have reached maturity by the
youngest age-group and therefore significant differences in these patterns as a function of age were predicted. Whereas neurophysiological evidence of MSI across all of the age-groups was anticipated, whether this would uniformly translate to improvements in behavioral measures of MSI remained an empirical question. Performance-benefits from multisensory inputs have been shown to change over childhood (Bair et al., 2007; Barutchu et al., 2009; Collignon et al., 2008) and therefore it would be reasonable to expect a systematic relationship between age and the extent of MSI. However a recent behavioral study using a paradigm nearly identical to the present showed that although evidence for MSI was seen in individual children ranging in age from 6 to 11, it was not as consistent or as strong as in adults, and no systematic relationship between age and MSI was found (Barutchu et al., 2009). The present study, combining both behavioral and electrophysiological measures of MSI, affords the opportunity to ally evidence of functional neural reorganization with changes in behavior with respect to MSI. Further, characterizing neurodevelopmental changes in basic audiovisual integration from middle childhood through adolescence will provide an important starting point from which future studies can begin to examine the developmental course of multisensory processing in clinical populations such as autism and schizophrenia.

**Materials and Methods**

**Participants**

Forty-nine typically-developing children and adolescents aged 7-16 years old and 13 young adults participated in this study. In order to assess developmental changes in multisensory integration, the children were divided into the following three age-groups: 7-9 years (n=17; 9 females; mean age=8.59), 10-12 years (n=15; 9 females; mean age=11.47), and 13-16 years (n
An additional six individuals (four between the ages of 7-9, one 11 years of age, and one adult) were excluded from all behavioral and neurophysiological analyses because of percent hits below 74% (two standard deviations below the average), making it unclear if these individuals were maintaining attention sufficiently. Participants were screened for neurological and psychiatric disorders. The adults ranged in age from 20 to 29 years (mean age= 23.11; s.d.= 2.57; 7 females). Children were administered the Wechsler Abbreviated Scales of Intelligence (WASI) and those children with a Full Scale IQ below 85 were excluded. Audiometric threshold evaluation confirmed that all participants had normal hearing. All participants had normal or corrected-to-normal vision. Children and adolescents were recruited from a local junior high school and from a community sample obtained through friends and acquaintances of colleagues and college students. Adults were recruited through the college’s Psychology research subject pool and from a community sample. Before entering into the study, informed written consent was obtained from the children’s parents, and verbal or written assent was obtained from children. Informed written consent was obtained from adult participants. All procedures were approved by the Institutional Review Board of the City College of the City University of New York.

Stimuli

**Auditory alone.** A 1000 Hz tone (duration 60 ms; 75 dB SPL; rise/fall time 5 ms) was presented from a single Hartman Multimedia JBL Duet speaker located centrally atop the computer monitor from which the visual stimulus was presented.

**Visual alone.** A red disc with a diameter of 3.2 cm (subtending 1.5° in diameter at a viewing distance of 122 cm) appearing on a black background was presented on a monitor (Dell
Ultrasharp 1704FTP) for 60 ms. The disc was located 0.4 cm superior to central fixation along the vertical meridian (0.9° at a viewing distance of 122 cm). A small cross marked the point of central fixation on the monitor.

**Auditory and visual simultaneous.** The ‘auditory-alone’ and ‘visual-alone’ conditions described above were presented simultaneously. The auditory and visual stimuli were presented in close spatial proximity, with the speaker placed atop the monitor in vertical alignment with the visual stimulus.

**Procedures**

Participants were seated in a dimly lit room 122 cm from the monitor. In order to minimize excessive movement artifacts, participants were asked to sit still and keep their eyes focused on the small cross in the center of the monitor. Participants were given a response pad (Logitech Wingman Precision) and instructed to press a button with their right thumb as quickly as possible when they saw the red circle, heard the tone, or saw the circle and heard the tone. The same response key was used for all three stimulus types. These were presented with equal probability and in random order in blocks of 100 trials. Inter-stimulus Interval (ISI) varied randomly between 1000 and 3000 (ms) according to a uniform (square wave) distribution. Participants completed a minimum of 8 blocks; most completed 10. Breaks were encouraged between blocks to help maintain concentration and reduce restlessness or fatigue. Throughout the experimental procedure, children’s efforts and good behavior were reinforced with stickers and verbal praise.
Data acquisition and analysis

**Behavioral.** Button press responses to the three stimulus conditions were acquired during the recording of the EEG and processed off-line. Reaction times between 100 and 900 ms were considered valid. This window was used to avoid the double categorization of a response.

**Event-related potentials.** High-density EEG was recorded from 72 scalp electrodes (impedances <5 kΩ) at a digitization rate of 512 Hz using the BioSemi system (BioSemi, Amsterdam, Netherlands, www.biosemi.com). The continuous EEG was recorded referenced to a Common Mode Sense (CMS) active electrode and a Driven Right Leg (DRL) passive electrode. CMS and DRL, which replace the ground electrodes used in conventional systems, form a feedback loop, thus rendering them references (Leavitt, Molholm, Ritter, Shpaner, & Foxe, 2007). Offline, the EEG was re-referenced to an average of all electrodes and divided into 1000 ms epochs (200 ms pre- to 800 ms post-stimulus onset) to assess slow wave activity in the data and perform high-pass filtering of the data without distorting the epoch of interest, from -100 to 500 ms). For children, an automatic artifact rejection criterion of +/- 140 μV from -100 to 500 ms was applied offline to exclude epochs with excessive EMG. For adults, the automatic artifact rejection criterion was set at +/-100 μV from -100 to + 500 ms. To compute event-related potentials (ERPs), epochs were sorted according to stimulus condition and averaged for each participant. Average waveforms from the auditory-alone condition and the visual-alone condition were then summed for each participant. Baseline was defined as the epoch from negative 50 ms to 10 ms relative to the stimulus onset (as in Molholm et al., 2002). A low pass filter of 45 Hz with a slope of 24 db/octave was applied to the individual averages to remove the high-frequency artifact generated by nearby electronic equipment. A high pass filter of 1.6 Hz with a slope of 12 db/octave was applied to the individual averages to remove ongoing slow-
wave activity in the signal, which otherwise would be doubly represented in the sum unisensory response when assessing MSIs (Molholm et al., 2002; Teder-Salejarvi, W. A., McDonald, Di Russo, & Hillyard, 2002). For each of the age-groups, group-averaged ERPs were calculated to view the waveform morphology of the three stimulus conditions and the sum condition.

**Statistical Analyses**

**Behavioral.** A two-way mixed design ANOVA (with factors of age-group and stimulus condition) was performed to compare the reaction times of the three stimulus conditions and to assess the effect of age on reaction time. Planned comparisons between each of the unisensory conditions and the multisensory condition were performed to test for the presence of a Redundant Signal Effect (RSE; in this case indicating behavioral facilitation for the multisensory condition compared to each of the unisensory conditions). A test of Miller’s Race Model (Miller, J., 1982) was then implemented. According to the Race Model, mean reaction times shorten because there are now two inputs (in this case auditory and visual) to trigger a response, and the fastest one wins. In this case facilitation can be explained in the absence of interaction between the two inputs. However, when there is violation of the Race Model it is assumed that the unisensory inputs interacted during processing to facilitate reaction time performance.

**Testing the Race Model.** Miller’s (1982) Race Model places an upper limit on the cumulative probability (CP) of reaction time at a given latency for stimulus pairs with redundant targets (i.e., targets indicating the same response). For any latency, \( t \), the Race Model holds when this CP value is less than or equal to the sum of the CP from each of the single target stimuli (the unisensory stimuli) minus an expression of their joint probability. For each subject, the reaction time range within the valid reaction times (in this case 100–900 ms) was calculated
over the three stimulus types (‘auditory-alone’, ‘visual-alone’, and ‘multisensory’) and divided into quantiles from the 5th to 100th percentile in 5% increments (5%, 10%, . . . , 95%, 100%). Violations were expected to occur for the quantiles representing the lower end of the reaction times, because this is when it was most likely that interactions of the visual and auditory inputs would result in the fulfillment of a response criterion before either source alone satisfied the same criterion (Miller, J., 1982). It should be noted here that failure to violate the Race Model is not evidence that the two information sources did not interact to produce response time facilitation, but rather it places an upper boundary on reaction time facilitation that can be accounted for by probability summation.

While reaction time performance was the main focus of the behavioral analysis, percent hits, defined as the percent of trials in which a response occurred within the valid reaction time range, were also calculated for each stimulus condition for all participants. A two-way mixed design ANOVA was performed to examine the effect of stimulus condition and age-group on percent hits.

**Event-related potentials.** As in previous work (e.g., Foxe et al., 2000; Giard & Peronnet, 1999; Molholm et al., 2002; Molholm et al., 2006), audiovisual interactions were measured by summing the responses to the ‘auditory-alone’ condition and the ‘visual-alone’ condition and comparing that ‘sum’ waveform to the response to the ‘multisensory’ audiovisual condition. Based on the principle of superposition of electrical fields, any significant divergence between the ‘multisensory’ and the ‘sum’ waveforms, indicates that the auditory and visual inputs interacted. (It should be noted that using this non-invasive far-field recording method we are entirely reliant on non-linear summation for evidence of multisensory interactions. As has been pointed out by Stanford and Stein (2007), a large proportion of multisensory neurons
respond with straightforward linear properties – that is, the multisensory response is a simple sum of the unisensory constituents.) To date, this common method of measuring AV multisensory processing by comparing the ‘multisensory’ and ‘sum’ ERPs has only been applied to adult data (Giard & Peronnet, 1999; Molholm et al., 2002; Talsma, D & Woldorff, 2005; Teder-Salejarvi, W. A. et al., 2002). This left little guidance from the literature for constraining the analyses. To constrain the analyses independent of the dependent measure (the difference between the multisensory response and the sum response), the temporal windows of analyses and electrodes to be tested were defined based on the peaks of the grand-mean ‘multisensory’ (audiovisual) responses. This approach has been applied to a number of high-dimensional data-sets from our laboratory as well as others (Russo et al., 2010; Wylie, Javitt, & Foxe, 2003), and while conservative, it provides a reasonable approach to delimiting the statistical tests to be performed on an a priori basis. Since there are well-known developmental changes in auditory and visual evoked-potentials, the time windows and electrodes tested were defined separately for each age-group. This resulted in six pre-defined peaks (see Table 3) which had similar spatio-temporal properties to the dominant underlying unisensory componentry (auditory P1, N1-frontocentral, N1-lateral, and P2; and the visual P1 and N1). For each of these time-windows, data from the 'multisensory' and 'sum' ERPs were submitted to a three-way mixed-design analysis of variance (ANOVA) with factors of stimulus type ('multisensory' versus 'sum'), scalp region (1-2 regions), and group (4 age-groups). Each scalp region was represented by the average amplitude over 2-5 electrodes. Greenhouse-Geisser corrections were used in reporting p-values when appropriate.

In addition to the highly conservative approach to data-analysis described above, a second, more comprehensive approach was employed. In this second phase of data exploration,
cluster-maps were generated for each age-group: Point-wise running paired $t$-tests (two-tailed) between the multisensory and sum responses were performed at each time-point, on data from each of the electrodes. Differences were only considered when at least 10 consecutive data points ($= 19.2$ ms at 512 Hz sampling rate) met a 0.05 alpha criterion. This approach has the potential to provide a fuller description of the data, which can also serve for hypothesis generation for future studies. The suitability of this method for assessing reliable effects and controlling for multiple comparisons is discussed elsewhere (Molholm et al., 2002; Murray, M M, Foxe, Higgins, Javitt, & Schroedrer, 2001).

**Results**

**Behavioral**

A two-way mixed design ANOVA revealed a main effect of Age-Group on Reaction Time ($F(3, 58) = 4.346, p<.01$), due to faster reaction times as age increased. There was also a main effect of stimulus Condition ($F(2, 116) = 176.052, p<.01$). This reflected faster reaction times to the multisensory condition compared to either the auditory-alone or visual-alone conditions. There was no interaction between Age-Group and stimulus Condition, and as can be seen in Figure 1, reaction time followed a similar pattern across the four age-groups. Planned comparisons between each of the two unisensory conditions and the multisensory condition (Table 1) confirmed the presence of a robust Redundant Signal Effect (RSE) in all age-groups. Individual subject analysis comparing the reaction time to each of the unisensory conditions with the reaction time to the multisensory condition revealed a RSE, whereby performance was significantly faster for the multisensory condition compared to the fastest unisensory condition.
RSE was observed on an individual basis for all but two children (one in the 7-9 year age-group, and one in the 10-12 year age-group).

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<td>Group data from t-tests comparing mean reaction times with the multisensory stimulus condition and each of the unisensory stimulus conditions (auditory-alone and visual-alone)</td>
</tr>
<tr>
<td>Age-group</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>7- to 9-year olds</td>
</tr>
<tr>
<td>10- to 12-year olds</td>
</tr>
<tr>
<td>13- to 15-year olds</td>
</tr>
<tr>
<td>Adults</td>
</tr>
</tbody>
</table>

Note: All 4 predefined age-groups responded significantly faster to the multisensory stimulus condition than to either of the unisensory stimulus conditions.

**Figure 1.** Mean reaction times (and SD) for auditory (A), visual (V), and AV conditions across age-groups.
Percent hits followed a pattern that was similar to that of the reaction time data. A two-way mixed design ANOVA revealed a main effect of Age-Group on Percent Hits \((F(3,58)=10.727, p<.01)\), due to higher percent hits as age increased (Table 2). There was also a main effect of stimulus Condition \((F(2,116) = 129.570, p<.01)\). This reflected higher percent hits to the multisensory condition compared to either the auditory-alone or visual-alone conditions. Age-Group and stimulus Condition interacted \((F(6, 116)=2.649, p=.019)\), because adult performance reached ceiling and therefore did not differ as a function of stimulus condition. Percent hits for each of the stimulus conditions for each of the age-groups are reported in Table 2.

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Percent hits (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multisensory</td>
</tr>
<tr>
<td>7- to 9-year olds</td>
<td>93 (4.32)a</td>
</tr>
<tr>
<td>10- to 12-year olds</td>
<td>96 (4.86)a</td>
</tr>
<tr>
<td>13- to 16-year olds</td>
<td>97 (3.68)a</td>
</tr>
<tr>
<td>Adult</td>
<td>99 (0.65)</td>
</tr>
</tbody>
</table>

Note: Percent hits to the auditory-alone condition did not differ significantly from percent hits to the visual-alone condition for any of the age-groups.

\(^{a}\)Percent hits to the multisensory condition are significantly higher than to either of the unisensory conditions \((P \leq 0.05)\).

**Testing the race model.** Individual subject analysis of the reaction time distributions revealed violation of the race model for all but six children. Five of these children were from the 7-9 year age-group (the youngest age-group), and one was from the 10-12 year age-group. To
test the reliability of these violations, the data from each of the age-groups for each of the quantiles (corresponding to the cumulative distribution of the fastest to the slowest reaction times, over 20 “quantiles”) were submitted to a *t*-test. These revealed significant race model violations in the 10-12 year olds, the 13-16 year olds, and the adults, but not in the 7-9 year old age-group, due to variability in the quantile in which violation was seen (Figure 2). In the 10-12 year olds group violations of the race model reached significance over the fourth quantile, in the 13-15 year old group over the fourth, fifth, and sixth quantiles, and in the adult group over the third, fourth, and fifth quantiles. A post-hoc ANOVA of race model violation in the 4th quantile, where it was most consistently violated across the participants in all age-groups, yielded a main effect of age-group (*F*(3,61) = 6.007, *p* = .001), with Fisher's LSD showing that the two oldest groups exhibited significantly more violation than the two youngest groups.

**Figure 2.** Miller inequality for the 4 age groups. Violations greater than zero signify violation of the race model. Arrows indicate the approximate location of the fourth quantile, race model was most consistently violated.
**Electrophysiological Data**

*Unisensory responses.* In all age-groups the ‘auditory-alone’ ERP was characterized by the typical P1-N1-P2 complex; however, the timing and topography of these components varied with respect to age (see Figure 3a). Specifically, the peak latency of the fronto-centrally focused auditory P1 moved earlier as age increased, peaking at 80 ms in the 7-9 year olds, 74 ms in the 10-12 year olds, 68 ms in the 13-16 year olds, and 40 ms in adults. Additionally, the amplitude of the auditory P1 component was larger in the two younger groups than in the older groups which is consistent with previous findings of larger P1 amplitude in children around 9-10 years of age (Ceponiene, Rinne, & Naatanen, 2002; Ponton, Eggermont, Kwong, & Don, 2000). In accordance with previous findings (e.g., Ceponiene et al., 2002), the auditory N1 was largest at fronto-central sites for the three oldest groups (the adults, 13-16 and 10-12 year olds), peaking at approximately 105 ms in these three groups. In contrast, the fronto-centrally focused auditory N1 in the youngest group (7-9 year olds) appeared smaller and slightly later than in the older age-groups, peaking at approximately 115 ms. The lateral N1 appeared largest and most well-defined in the younger groups, peaking at approximately 170 ms in the 7-9 year olds and at 165 ms in the 10-12 year olds (e.g., Gomes et al., 2001). In the 13-16 year olds and the adults, the relatively small lateral N1 peaked at approximately 160 ms and 150 ms, respectively. The auditory P2 was centrally focused with a similar latency peak amplitude across the groups (180 ms in the 7-9 and 10-12 year old groups, at 165 in the 13-16 year old group, and at 175 ms in the adults).
Figure 3. Grand averaged unisensory auditory and visual ERPs are depicted in panels (a) and (b), respectively, for the 4 age-groups. Auditory-alone responses are shown from representative frontocentral and frontotemporal electrode sites (FT7, FT8, and FCz) and visual-alone responses from representative occipital sites (PO7, PO8, and Oz).
The overall morphology of the response elicited by the visual-alone stimulus was quite similar across age-groups. There was a reduction in overall amplitude as age increased and there were small changes in the peak latencies of the P1 and N1 responses (see Figure 3b), as is typically observed in developmental data (e.g., Lippe, Roy, Perchet, & Lassonde, 2007). The visual P1 appeared maximal over occipital regions in the three pediatric groups, peaking at approximately 140 ms in the 7-9 year old group, 145 ms in the 10-12 year old group, and 127 ms in the 13-16 year old group. In adults, the visual P1 was more parietally focused and peaked at approximately 137 ms. The timing of the P1 was somewhat later than typical; since the difference was seen across all age-groups this is likely due to stimulation parameters. The visual N1 was focused over lateral occipital electrode sites and peaked between 182-207 ms, with latency decreasing as a function of age. The developmental trajectories of auditory and visual sensory responses have been described and analyzed in great detail elsewhere (e.g., Ceponiene et al., 2002). These unisensory “components” (P1, N1, etc…) are thought to represent distinct processing stages and to reflect multiple sources of neuronal generators within the relevant primary and association cortices (auditory cortical regions for the auditory componentry and visual cortical regions for the visual componentry) (e.g., Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2002; Foxe & Simpson, 2002; Naatanen & Picton, 1987). It is also assumed that the complexity of the information extracted from the signal increases as a function of the increasing latency of the responses (Foxe & Simpson, 2002; Murray, M.M., Imber, Javitt, & Foxe, 2006). Since these developmental data on unisensory responses appear highly similar to those reported in earlier studies and the focus of this investigation is on multisensory processing, they are not considered further.
Multisensory responses. In the audiovisual response, 6 distinct spatio-temporal patterns between 0 and 250 ms were readily identified. These were similar to the auditory and visual unisensory componentry described above, and similarly varied across age-groups in their precise timing and topography. These spatio-temporal patterns were used to define the time-windows and scalp regions used to test for multisensory effects, and are delineated in Table 3 for each of the age-groups. ‘Multisensory’ and ‘sum’ ERPs were compared using separate mixed-design ANOVAs with the between subjects factor of Age-Group, and the within subjects factors of Condition (‘sum’ vs. ‘multisensory’) and Region. For the analysis of data around the time and region of the fronto-central auditory N1 (fronto-central, 95-138 ms), there was a significant main effect of Condition ($F(1, 58) = 6.591, p=.013$) and an interaction of Condition and Age-Group ($F(3, 58) = 3.966, p=.012$). Follow-up tests revealed that the amplitude of the multisensory response was significantly more negative than that of the sum response in the two oldest age-groups (13-16 year olds and adults), but not in the two younger age-groups. Observationally, this pattern was reversed for the youngest group (7-9 year olds) such that the amplitude of the sum response was more negative than that of the multisensory response, but this difference was not significant at the tested latency. Electrode Fz best illustrates this fronto-central Condition by Age-Group interaction, at about 100-140 ms (see Figure 4 where the effect is highlighted; and also Figures 5-8). Scalp voltage maps of this effect revealed highly similar scalp distributions for the three oldest age-groups, with a stable positive-negative configuration suggestive of primary neural sources in parietal cortex (see Figure 4). The negative portion of this configuration had a slightly leftward bias. The data from the youngest age-group did not conform to this pattern; since this effect was not significant, we do not describe it further. The auditory-alone voltage maps are illustrated at the same latencies for comparison, and show a clearly
different distribution that is consistent with neural sources in the temporal lobe in the region of auditory cortex for the three oldest groups. For the youngest group the auditory-alone response was close to baseline at the tested latency and hence does not show an interpretable distribution. In the latency and region of the auditory P2 (fronto-central, 165-210 ms), a marginal trend was noted for the interaction between Condition and Age-Group \( (F(3, 58) = 3.548, p = .065) \), which post-hoc tests revealed was associated with a significant difference between the amplitude of the multisensory and sum response in only the adult group \( (p = .026) \). Finally, there was a main effect of condition around the latency and region of the visual N1 (parieto-temporal-occipital region, 166-210), with the multisensory response more negative-going than the sum response \( (F(1, 58) = 4.280, p = .045) \); this effect is illustrated in Figures 5-8 and Supplementary Figure 1 in electrodes O1 and O2). No additional main effects or interactions involving the factor of Condition were revealed by these analyses.

<table>
<thead>
<tr>
<th>Peak</th>
<th>Corresponding sensory component</th>
<th>Regions of analysis (electrodes)</th>
<th>Time windows ( ^a ) tested in each age-group</th>
<th>Note: The time windows, regions, and electrodes were chosen based on the morphology of the multisensory ( (AV) ) grand-averaged ERPs for each age-group.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Auditory P1</td>
<td>Frontal ( (AFz, Fz, F1, F2) )</td>
<td>66-96, 64-94, 56-74</td>
<td>90-59</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Auditory N1</td>
<td>Frontocentral ( (FCz, FC1, FC2, ECz) )</td>
<td>116-138, 100-130, 100-120, 95-115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Auditory N1</td>
<td>Left temporal ( (T7, T5, T9) )</td>
<td>143-160, 150-170, 142-162, 136-158</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Auditory P2</td>
<td>Right temporal ( (T8, T6, TP9) )</td>
<td>160-180, 154-184</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Visual P1</td>
<td>Frontocentral ( (FCz, FC1, FC2, CZ) )</td>
<td>192-210, 187-207, 172-192, 165-185</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Visual N1</td>
<td>Occipital ( (O1, O2, OZ) )</td>
<td>140-150, 138-158, 115-135, 115-135</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left parietooccipital ( (PO3, PO7) )</td>
<td>140-150, 138-158, 115-135, 115-135</td>
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<tr>
<td></td>
<td></td>
<td>Right parietooccipital ( (PO4, PO8) )</td>
<td>140-150, 138-158, 115-135, 115-135</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left ( TPO^d ) ( (O1, P7, P8, P9, T9, TP7) )</td>
<td>192-210, 183-213, 176-196, 168-186, 168-186</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right ( TPO^d ) ( (O2, P8, PO9, PO8, TP9) )</td>
<td>192-210, 183-213, 176-196, 168-186, 168-186</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Time is measured in ms.
\( ^d \) Parieto-temporal-occipital region.
Figure 4. For each of the 4 age-groups, the grand-averaged ERPs for the multisensory (black) and sum (red) responses at electrode Fz (location indicated by a black dot) are depicted on the left side of the figure. The response from ~100--140 ms is enlarged to show the group by condition interaction effect. On the right side, voltage maps depict the scalp distribution of this effect (i.e., the difference between the multisensory and sum responses) and the corresponding auditory-alone response within the latencies used in the ANOVA and correlation analysis.
Figure 5. Grand-averaged ERPs for the multisensory (black) and sum (red) responses for the 7- to 9-year-old age-group.
Figure 6. Grand-averaged ERPs for the multisensory (black) and sum (red) responses for the 10- to 12-year-old age-group.
Figure 7. Grand-averaged ERPs for the multisensory (black) and sum (red) responses for the 13- to 16-year-old age-group.
Figure 8. Grand-averaged ERPs for the multisensory (black) and sum (red) responses for the adult age-group.

Cluster based t-tests on the multisensory versus sum responses. A more comprehensive picture of the spatial-temporal characteristics of the audiovisual interactions can be gained from the secondary analysis in which restricted cluster plots were generated from t-tests performed between the multisensory and sum conditions for all scalp electrodes for data-points from 0-300 ms post-stimulus onset (Figure 9). Three main clusters of AV interactions were apparent, although not all were observed in each of the age-groups. In contrast to an early study using a
highly similar paradigm (Molholm et al., 2002), no early MSIs (earlier than 100 ms) were observed in our adult group in the cluster plot analysis, even when the statistical criterion was relaxed from 10 to just 5 consecutive significant data points. We suspect that this lack of early MSI (at least in our adult group) reflects paradigm differences between the studies. (In their 2002 study, Molholm and colleagues titrated the location of stimulus presentation so that a robust C1 visual response was observed on an individual subject basis, whereas this procedure was not followed here due to the time constraints imposed by working with a pediatric population.) Consistent with the primary analysis, AV interactions were seen over fronto-central scalp regions from about 100-120 ms in the cluster plots of the youngest group and the two older groups (the 13-16 year olds and the adults), but not in the 10-12 year old group. Examination of the waveforms (electrode Fz, Figure 4) clarifies that the frontal AV interactions seen in the cluster plot of the 7-9 year old group are in the opposite direction (with ‘sum’ more negative than ‘multisensory’) than for the other age-groups. The cluster plots reveal an additional pattern of AV interactions in the 100-150 ms time window over parietal scalp in the two older groups (the 13-16 year olds and the adults), but not in the two younger groups (see electrode Pz in Figures 5-8). The next clear AV interactions were seen between 190-240 ms. In the adult group interactions in this timeframe were widespread, appearing over anterior, central and parietal regions (see for example Figure 8, electrodes C1, C2, and Pz). Consistent with the a priori analysis, the adult group also exhibited AV interactions over fronto-central scalp in this time frame. The interactions at around 200 ms were somewhat lateralized over frontal and central regions in the three child age-groups (see FC5 and FC6 in Figures 5-8, perhaps explaining why they were not picked-up in the a priori analysis (“auditory P2” test). The cluster plots reveal an additional region of AV interactions around 200 ms in the 7-9 year olds over parietal scalp
regions (Figure 5, electrode Pz). Finally, all four groups showed wide-spread AV interactions over multiple scalp regions from 275 ms onward. This most likely reflects cortical activity related to the motor responses made following the occurrence of a stimulus. In this time-frame the sum response, where the supposed motor-related activity is represented twice, was larger.

**Correlation Analysis.** *A post hoc* correlation analysis was performed to test for a relationship between the behavioral and neurophysiological measures of audiovisual integration. Specifically, *a* correlation between race model violation in the 4th quantile, where the race model was most consistently violated across the full set of participants, and the difference between the ‘multisensory’ and ‘sum’ evoked potentials in the fronto-central region between 95-138 ms, was computed (the same temporal window and scalp regions used for the ANOVAs- see Table 3). This revealed a significant correlation of .35 (*r*(60)=.352, *p*=.005). To see how this might be related to stage of development, we also examined if race model violation was related to age, and found a significant correlation of .48 (*r*(60)=.478, *p*<.001).
Figure 9. Significant P values over time for 64 scalp electrodes from running t-tests comparing the multisensory and sum ERPs for each of the 4 age-groups. Differences between the 2 conditions were only considered when at least 10 consecutive data points (519.2 ms at 512 Hz sampling rate) met a 0.05 alpha criterion. P values are differentiated with the color scale shown to the right. Blue indicates an absence of significant P values. Time is plotted on the x-axis from 0 to 300 ms. Electrodes are plotted on the y-axis. Starting from the bottom of the graph, the electrodes are divided into sections from posterior to anterior scalp. Each color represents 4–5 electrodes, the relative positions of which are located on the corresponding head shown to the left. Solid gray boxes around 100 ms and 200 ms indicate the 2 main time windows discussed in the text.
Discussion

Just how the human brain integrates multisensory information during the childhood years, and how this develops over time, has not been well-characterized to date. Here we undertook a cross-sectional investigation to examine the developmental trajectory of audiovisual MSI, using related electrophysiological and behavioral metrics and sampling from 4 age-groups from 7 years of age to adulthood. These data revealed maturation in the manner in which very basic auditory and visual stimuli are integrated during a simple reaction time task, both in terms of facilitation of behavior and in terms of the underlying neural processes.

For the behavioral data, simply looking at mean reaction times, all groups exhibited a significant speeding of response time when the visual and auditory stimuli were presented simultaneously compared to when they were presented alone. Since behavioral facilitation can result from probability summation however, race model violation was used as a test of whether multisensory processing had contributed to performance facilitation. This indicated that multisensory facilitation of behavior was still clearly immature at 8 years of age (in the 7-9 year old group), but seemed to have reached mature levels by about 15 years of age, with similar patterns of facilitation and race-model violation for the 13-16 year group and the adult group (see Figure 2). A more complete picture of the development of multisensory facilitation can be gathered by considering the individual subject data as a function of age-group. On an individual basis, all of the participants in the two oldest age-groups (13-16 years and adults) demonstrated race model violation. Further, across these two groups the magnitude of violation was highly similar, as suggested in Figure 2 and by the follow-up test on data from the 4th quantile. In contrast, for the youngest group race-model violation was only seen in 12 of the 17 participants, and for these 12 the magnitude of violation tended to be very small, and was variable across
participants in terms of where in the reaction time distribution it was seen (resulting in no effect across participants, see Figure 2). For the 10-12 year olds, the second to youngest age-group examined, there was significant race model violation in all but one participant, but like the youngest group, violation was of lesser magnitude than for the two older groups of participants, and there was greater variability in terms of where in the reaction time distribution violation was seen. Thus from the behavioral data there appears to be a gradual fine-tuning of the ability to benefit from the simultaneous presentation of auditory and visual response cues. Using a very similar paradigm, Barutchu and colleagues (2009) failed to find a consistent increase in race model violation as a function of age for children from 6 to 11 years of age. In their data there was no evidence for race model violation in the 10-11 year old age-group, nor in the 6 year olds, but there was in the intervening age groups and in adults. There were similarities to the present findings insofar as race model violation was observed to be smaller and more variable for the children compared to a group of young adults. The failure to observe as systematic a relationship as was seen here might be due to a difference in how the test of the race model was instantiated. Whereas here the reaction time distribution was divided into 20 quantiles and the percent of responses that fell into each determined on a within subject basis, as we have done in previous tests of the race model (Molholm et al., 2004; Molholm et al., 2002; Murray, M. M., Molholm, et al., 2005), Barutchu and colleagues fit the reaction times to only 10 probability values, from .05 to .95. Further, these researchers presented just 40 stimuli of each class (120 total) in their experiment, which would provide only 4 trials of each stimulus type per decile, whereas participants in this study received a minimum of 335 trials of each type (>1000 total).

In line with the behavioral findings, brain measures of audiovisual integration also indicated a systematic relationship between age-group and multisensory processing. This was
clearly evident in the time-frame of the fronto-centrally focused auditory N1. Here, in the youngest group, the multisensory response was less negative-going than the sum response, whereas this relationship was shifted for the two oldest age-groups such that the multisensory response was clearly more negative-going (Figure 4). In the intervening age-group of 10-12 year-olds the multisensory response was just barely more negative going than the sum response (Figure 4), suggestive of a transitional stage. These data showed a significant positive correlation with the behavioral measure of MSI, suggesting that the underlying brain processes (or a subset of the brain processes) contributed to the observed multisensory behavioral facilitation.

Examination of the scalp distribution of this MSI-effect in the time frame of the auditory N1 suggested parietal generators for the three oldest age-groups. The parietal region is known to play a key role in the integration of multisensory inputs in both humans and in non-human primates. The intraparietal sulcus (IPS) in particular has been implicated in multisensory processing across a number of paradigms, types of stimuli, and sensory combinations (e.g., auditory, visual, tactile, and proprioceptive inputs). This region is involved in sensory-motor transforms and the coordination of multiple spatial-reference frames (e.g., retinotopic, somatotopic, etc.) (e.g., Anderson, R. A., Snyder, Bradley, & Xing, 1997; Mullette-Gillman, Cohen, & Groh, 2009), and has been shown to be part of neural networks involved in the processing of audiovisual speech (e.g., Benoit, Raji, Lin, Jaaskelainen, & S., 2010), cross-modal spatial attention (e.g., Macaluso, Eimer, Frith, & Driver, 2003; Teder-Salejarvi, W.A., Munte, Sperlich, & Hillyard, 1999), audiovisual object recognition (Werner & Noppeney, 2010) and visuo-haptic object recognition (Kim & James, 2010) among other multisensory processes (see for example, Calvert, 2001). The superior portion of the parietal lobe (SPL) is also involved in
multisensory processing and it has been suggested that in humans this may represent the homologue of a portion of IPS in non-human primates (Molholm et al., 2006; Moran, Molholm, Reilly, & Foxe, 2008). The protracted maturation of cortical MSI seen in these data may also be related to the maturational trajectories of the underlying unisensory systems. For example, while the inner ear and brainstem auditory structures are remarkably well-developed at birth and reach maturity by about 6 months of age, based on changes in the P1 and N1 of the auditory evoked response it has been argued that the maturation of auditory cortex is a decade-long process that extends into adolescence (based on changes in the auditory evoked response, e.g., Moore & Linthicum, 2007; Ponton et al., 2000). Obviously if there is not a stable unisensory input-output function, this could impact processes into which these data feed (e.g., multisensory integration processes). Another possibility, not mutually exclusive with the above, is that such protracted maturation relates to the need for prolonged plasticity in order to gain from the local statistical relationships among the many multisensory inputs that are encountered on a daily basis (e.g., Yu, Rowland, & Stein, 2010). This fits well with evidence for changes in how multisensory inputs are weighted over development (Collignon et al., 2008) as well as preliminary data from our lab which suggest developmental changes in the extent of multisensory gain compared to unisensory stimulation.

Though not specifically investigated to date, well-known developmental changes in attentional capacity (Konrad et al., 2005; Paus, Babenko, & Radil, 1990; Posner & Rothbar, 1998) are likely to play a significant role in the ability to use multiple information sources and therefore in how different sensory inputs are weighted during the performance of a task. The possibility that maturational differences in attentional capacity may have contributed to some of the differences in MSI observed in the current study is in line with our behavioral data in which
overall performance improved with age. However, differences in performance could reflect a number of variables including maturational effects on processing speed (Fry & Hale, 2000; Kail, 1991; Luna, Garver, Urban, Lazar, & Sweeney, 2004), the development of higher-order goal directed planning and execution of behavior (Anderson, P., 2002; Luciana, Conklin, Hooper, & Yarger, 2005; Welsh, Pennington, & Groisser, 1991), and attention. Future work will be required to parse these potential contributions to the maturation of multisensory processing.

Higher-order perceptual processes such as object and speech recognition depend on intact lower-level sensory processing (Doniger, G.M., Silipo, Rabinowicz, Snodgrass, & Javitt, 2001; Fitch & Tallal, 2003; Leitman et al., 2007); if the cortico-cortical pathways that mediate basic multisensory processing are in a state of fluctuation throughout middle childhood as suggested by the current neurophysiological findings, then subsequent stages of multisensory processing that are responsible for object and speech recognition are likely affected. Given the apparent ease with which typically-developing children recognize multisensory objects and speech, it is tempting to assume that the sensory and perceptual processes that underlie this fundamental skill are mature by middle childhood. However, the data here suggest that the basic brain processes, needed to support multisensory object processing, speech recognition, are not the same in children as in adults. These important perceptual processes may be less automatic in children and may rely more heavily on later, more effortful stages of multisensory processing.

While the electrophysiological data afforded a straightforward interpretation of multisensory processes in the timeframe of the fronto-central auditory N1, this was not so clearly the case for the next prominent multisensory modulation at about 200 ms post stimulus onset. The a priori test corresponding to the timing and topography of the visual N1 showed a main effect of condition and no interaction with group, but consideration of the cluster maps indicated
that modulation in this timeframe was most evident in the youngest and oldest age-groups (7-9 years and adults), and showed very different distributions for each (Figure 9). These showed that audiovisual interactions around 200 ms were widespread in adults, appearing across frontal, central, and parietal areas. In the 7-9 year old age-group, effects between about 180-220 ms were primarily observed over parietal and occipital regions. One possible explanation for the differential MSI effects relates to their falling within the timeframe that is associated with automatic visual “object recognition” processes (based on electrophysiological studies; e.g., Doniger, G.M., Foxe, et al., 2001; Murray, M. M., Foxe, & Wylie, 2005). Given this, it may be that the inputs are treated as objects by the youngest age-group, resulting in processing focused over visual scalp regions (though not focused over more lateral posterior scalp regions as might be expected for object processing), and as potential objects by the oldest, resulting in a more widespread activation that includes higher-order frontal areas. Such differences could reflect developmental changes in degrees of specialization of object processing. Granted somewhat speculative, this possible explanation of the data is put forth in the spirit of generating models of the development of multisensory processing for directed hypothesis testing.

Conclusion

With the use of behavioral probes it has been established that in humans the processes underlying multisensory integration continue to mature well into middle childhood, if not beyond this stage of development. To the best of our knowledge, however, the underlying changes in brain activity that must accompany changes in behavior have not been previously documented. Here electrophysiology was used to characterize the developmental trajectory of the brain processes underlying audiovisual multisensory processing over middle childhood, and to ally this with developmental changes in the extent to which auditory and visual cues are integrated to
speed performance in a simple reaction time task. The data show that changes in the brain processes underlying multisensory integration in the 100 to 120 ms timeframe are systematically related to increased multisensory gains in performance (as indexed by race model violations), with the latter increasing as a function of age. This is consistent with protracted plasticity in a dynamic system that continues to update the relative significance of multidimensional inputs from the environment. These data provide an important point of reference, against which to assay the development of multisensory processes in clinical populations where integration problems are suspected.
CHAPTER 2
The Development Of Multisensory Integration In High-Functioning Autism: High-Density Electrical Mapping And Psychophysical Measures Reveal Impairments In The Processing Of Audiovisual Inputs

Abstract

Successful integration of auditory and visual inputs is crucial for both basic perceptual functions and for higher-order processes related to social cognition. Autism spectrum disorders (ASD) are characterized by impairments in social cognition and are associated with abnormalities in sensory and perceptual processes. Several groups have reported that individuals with ASD are impaired in their ability to integrate socially relevant audiovisual (AV) information, and it has been suggested that this contributes to the higher-order social and cognitive deficits observed in ASD. However, successful integration of auditory and visual inputs also influences detection and perception of nonsocial stimuli, and integration deficits may impair earlier stages of information processing, with cascading downstream effects. To assess the integrity of basic AV integration, we recorded high-density electrophysiology from a cohort of high-functioning children with ASD (7–16 years) while they performed a simple AV reaction time task. Children with ASD showed considerably less behavioral facilitation to multisensory inputs, deficits that were paralleled by less effective neural integration. Evidence for processing differences relative to typically developing children was seen as early as 100 ms poststimulation, and topographic analysis suggested that children with ASD relied on different cortical networks during this early multisensory processing stage.
**Introduction**

Autism spectrum disorders (ASD) are characterized by impairments in social communication and by restricted, repetitive and stereotyped behavioral patterns (American Psychiatric Association, 2000). Unusual sensory symptoms, though not included in the current diagnostic formulation, have long been noted in individuals with ASD (Asperger, 1944; Ayres & Tickle, 1980; Ben-Sasson et al., 2009; Bergman & Escalona, 1949; Cheung & Sui, 2009; Crane, Goddard, & Pring, 2009; Hermelin & O'Connor, 1970; Kanner, 1943; Kern et al., 2006; Kern et al., 2007; Kientz & Dunn, 1997; Lane, Dennis, & Geraghty, 2010; Lane, Young, Baker, & Angley, 2010; O'Neill & Jones, 1997; Wing, 1969). Anecdotal and clinical reports suggest that individuals with ASD may also have problems integrating sensory information (O'Neill & Jones, 1997). Given that fundamental functions such as detecting and localizing an object, as well as higher-order processes such as object identification and social communication (e.g., speech and emotion recognition), are enhanced by complementary multisensory inputs (Fiebelkorn et al., 2011; Gingras, Rowland, & Stein, 2009; Molholm et al., 2004; Molholm et al., 2002; Ross, L. A. et al., 2011; Ross, L. A., Saint-Amour, Leavitt, Javitt, et al., 2007; Ross, L. A., Saint-Amour, Leavitt, Molholm, et al., 2007; Stein, B., Meredith, Huneycutt, & McDade, 1989; Stein, B. E., Huneycutt, & Meredith, 1988; Werner & Noppeney, 2010), impairments in the ability to integrate multisensory information could have potentially devastating consequences for perceptual, cognitive, and social functioning (Foxe & Molholm, 2009).

A surge in investigations into multisensory influences on perception and cognition has led to significant progress in our understanding of how the brain processes and benefits from multisensory inputs (Foxe & Molholm, 2009; Foxe & Schroeder, 2005; Foxe et al., 2002; Klemen & Chambers, 2012; Stein, B. E., Stanford, Ramachandran, Perrault, & Rowland, 2009).
These insights combined with renewed interest in the role of sensory integration in autism have sparked research directed at empirically testing the basis of subjective reports of multisensory processing deficits in ASD (for a review, see Marco, Hinkley, Hill, & Nagarajan, 2011). The preponderance of this research has been behavioral, and has largely focused on the processing of multisensory audiovisual (AV) social stimuli related to communication, such as speech sounds accompanied by their requisite lip movements. Results from the majority of these studies indicate that the ability to integrate AV speech inputs is impaired in individuals with ASD (de Gelder et al., 1991; Irwin et al., 2011; Magnee, de Gelder, van Engeland, & Kemner, 2008; Mongillo et al., 2008; Smith & Bennetto, 2007; Taylor et al., 2010); but see Iarocci et al. (2010) and Williams et al. (2004). Only a few studies have considered AV integration in ASD for non-social stimuli (Foss-Feig et al., 2010; Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2011; Mongillo et al., 2008; van der Smagt et al., 2007), and these have yielded mixed and somewhat conflicting results. Thus the question remains as to whether impairments in AV integration are specific to complex social stimuli, which are by definition problematic in ASD, or if instead they are rooted in more basic deficits in multisensory processing. This has obvious implications for understanding the basis of impairments in higher-order cognitive processes in ASD (e.g., social communication), as well as for neurobiological theories of ASD such as the disordered connectivity account (Just, Cherkassky, Keller, & Minshew, 2004).

Decades of brain imaging research on the neural underpinnings of ASD strongly suggest that autism is not a strictly localized brain disorder, but rather a disorder involving multiple functional neural networks (Muller, 2007; Rippon, Brock, Brown, & Boucher, 2007). An accumulation of neuroanatomical and neurofunctional findings in ASD (see Courchesne, Redcay, Morgan, & Kennedy, 2005; Schipul, Keller, & Just, 2011) have lead to the proposal that
the common pathway to the ASD phenotype is disordered brain connectivity (Anagnostou & Taylor, 2011; Belmonte et al., 2004; Just et al., 2007; Wass, 2011). Disordered connectivity has obvious implications for the integration of information from the different "processing nodes" within a functional network, perhaps especially so when these segregate to anatomi

cally distant brain regions. Thus, whilst humans seamlessly integrate inputs from multiple sensory modalities to oftentimes dramatically influence perception and performance (Fiebelkorn et al., 2011; Ma et al., 2009; Ross, L. A., Saint-Amour, Leavitt, Javitt, et al., 2007; Wallace, Roberson, et al., 2004), dysfunctional patterns of brain connectivity, as proposed for ASD, should lead to deficits in the integration of multisensory cues.

The present study investigated whether children and adolescents with a diagnosis of ASD show evidence of multisensory dysfunction for the integration of basic AV inputs. Previous work from our laboratory characterized the typical developmental course of AV integration for such stimuli, from middle childhood to adulthood, using both behavioral and electrophysiological indices of multisensory integration (MSI; Brandwein et al., 2011). To address whether individuals with autism have general deficits in their integration of AV information independent of social or communication-related uses, we applied these well-defined metrics of MSI to a population of high-functioning children with a diagnosis of ASD. This allowed us to systematically assess the time course and underlying neuronal generators involved in the integration of simple AV stimuli in children with ASD, and whether these are related to the ability to benefit behaviorally from multisensory cues. Because development is known to strongly influence the extent to which multisensory cues influence perception and behavior (Bair et al., 2007; Brandwein et al., 2011; Flom & Bahrick, 2007; Gori et al., 2008; Hillock, Powers, & Wallace, 2011; Lewkowicz, D. J., 2003; Lewkowicz, D. J. & Ghazanfar, 2009; Neil et al., 2006;
Ross, L. A. et al., 2011; Stein, B. E. & Rowland, 2011), we additionally considered the developmental course of these processes in ASD by comparing data from younger (7-10) and older (11-16) children.

Materials and Methods

Participants

72 individuals with typical development (TD) and 46 individuals with ASD between the ages of 7 and 16 years participated. An additional 13 individuals (3 TD, 10 ASD) were excluded from all behavioral and electrophysiological analyses because of hit rates 2.5 standard deviations below the sample's average or for an excessive number of button presses making it difficult to know whether they were attending to the stimuli. 2 of the 118 individuals (1 TD, 1 ASD) that were included in the behavioral analyses were excluded from the electrophysiological analyses due to excessively noisy event-related potentials (ERP) data (i.e., fewer than 50% of trials per condition were accepted). Exclusionary criteria for both groups included a nonverbal IQ below 80 as assessed by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and a history of seizures or head trauma. All participants had normal or corrected-to-normal vision and passed a hearing screen. Exclusion criteria for the TD group included a history of developmental, psychiatric, or learning difficulties as assessed by a parent history questionnaire. All children were screened for attention deficit/ hyperactivity disorder (ADHD). Only TD children were excluded if their parents endorsed six items or more of inattention or hyperactivity on a DSM-IV ADHD behavioral checklist. Children with ASD were not excluded for presenting with symptoms of inattention and hyperactivity, as such symptoms are very common in ASD, and the DSM-IV holds that a diagnosis of an ASD precludes a comorbid diagnosis of ADHD. Children
with TD were also excluded if they had a biological first-degree relative with a known developmental disorder.

For the ASD group, diagnoses of ASD were obtained using both the Autism Diagnostic Interview-R (Lord, Rutter, DiLavore, & Risi, 1994) and the Autism Diagnostic Observation Schedule (Lord, Rutter, DiLavore, & Risi, 1999), and were confirmed by clinical judgment for 42 of the 46 children. Diagnoses of the remaining 4 children were made by a licensed clinical psychologist external to this study using the DSM-IV TR's diagnostic criteria for ASD. All but 2 of the 46 children in the ASD group had also been diagnosed by a licensed clinician (typically a psychiatrist, psychologist, or developmental pediatrician or neurologist) prior to entering the study. Of the 46 children in the ASD group, 13 had a diagnosis of Autistic Disorder, 24 of Asperger's Disorder, and nine of Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS). Parents were asked to refrain from giving their children (n=9) stimulant medication in the 24-hour period preceding the testing session. Six children were taking other psychoactive medications (including SSRIs, aripiprazole, atomoxetine, lithium, guanfacine, and risperidone) at the time of testing. To ensure that medication was not a confounding factor, analyses were also performed excluding these six medicated individuals. Because the main between group findings were maintained, the more inclusive analyses are reported.

In order to assess developmental changes in MSI, participants were divided into two age groups: 7-10 years and 11-16 years. Table 1 outlines participant characteristics. The distribution of males and females in the TD groups was fairly even (45% were male in the younger group and 49% were male in the older group), whereas the ASD groups consisted primarily of males (86% in the younger group and 79% in the older group), which is representative of the well-established male: female ratio (4:1) of ASD in the general population.
A comparison within the TD group of the dependent measures as a function of sex did not attain significance on our primary behavioral or electrophysiological measures of MSI. Further, in response to a reviewer’s suggestion, all between group analyses were performed on a smaller sample in which the sex ratio was matched between the ASD and TD groups (by excluding some of the females in the TD group). Because this yielded between group effects that were essentially identical to that for the larger sample, we report the results from the original analyses of the full dataset. Participants were group matched on the basis of Performance IQ (PIQ) and age. An ANOVA revealed that there were no significant differences between the TD and the ASD groups in PIQ (young: $F(1,53)=.076, p=.783$; old: $F(1,61)=.682, p=.412$) or in Age (young: $F(1,53)=.236, p=.629$, old: $F(1,61)=3.432 p=.069$).

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Younger children: 7–10 years</th>
<th>Older children: 11–16 years</th>
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<tbody>
<tr>
<td></td>
<td>TD</td>
<td>ASD</td>
</tr>
<tr>
<td>Age</td>
<td>9.0 (1.2)$^a$</td>
<td>9.2 (1.3)$^a$</td>
</tr>
<tr>
<td>VIQ</td>
<td>114 (14)</td>
<td>105 (20)</td>
</tr>
<tr>
<td>PIQ</td>
<td>109 (13)$^c$</td>
<td>110 (18)$^c$</td>
</tr>
<tr>
<td>FSIQ</td>
<td>113 (14)</td>
<td>108 (20)</td>
</tr>
<tr>
<td>M</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>No males</td>
<td>15</td>
<td>19</td>
</tr>
</tbody>
</table>

PIQ, performance intelligence quotient as measured by the Wechsler Abbreviated Scale of Intelligence (WASI). The PIQ of four children in the ASD group were measured using the Wechsler Intelligence Scale for Children (WISC-IV).

$^a,b$Age of participants was not significantly different.

$^c$PIQ of participants was not significantly different.

Before participating, informed written consent was obtained from every child’s parent or legal guardian, and verbal or written assent was obtained from each child. All procedures were
approved by the Institutional Review Boards of the City College of the City University of New York and the Albert Einstein College of Medicine. Participants were given $12.00 an hour for their time in the laboratory. All procedures were consistent with the ethical standards laid out in the Declaration of Helsinki.

**Procedure**

Participants performed a simple reaction time (RT) task at a computer in a dimly lit sound attenuated and electrically shielded room. The task was identical to that described in Brandwein and colleagues (2011) and consisted of three stimulus conditions presented in random order with equal probability. To decrease predictability of the timing of stimulus presentation, the inter-stimulus interval (ISI) varied randomly between 1000 and 3000 ms according to a uniform (square wave) distribution. Varying the ISI served to minimize the extent to which participants could predict and anticipate stimulus onset thus reducing the contribution of anticipatory potentials to the ERP (see Teder-Salejarvi, W. A. et al., 2002). The 'auditory-alone' condition consisted of a 1000-Hz tone (duration 60 ms; 75 dB SPL; rise/fall time 5 ms) presented from a single Hartman Multimedia JBL Duet speaker located centrally atop the computer monitor from which the visual stimulus was presented. The 'visual-alone' condition consisted of a red disc with a diameter of 3.2 cm (subtending 1.5° in diameter at a viewing distance of 122 cm) appearing on a black background and presented for 60 ms on a monitor (Dell Ultrasharp 1704FTP). The disc was located 0.4 cm above central fixation along the vertical meridian (0.9° at a viewing distance of 122 cm). The 'audiovisual' condition consisted of the 'auditory-alone' and 'visual-alone' conditions presented simultaneously. The auditory and visual stimuli were presented in close spatial proximity, with the speaker placed in vertical alignment with the visual stimulus. Participants were instructed to press a button on a response pad (Logitech Wingman
Precision) with their right thumb as quickly as possible when they saw the circle, heard the tone, or saw the circle and heard the tone. The same response key was used for all 3 stimulus types. Stimuli were presented in blocks of approximately 100 trials each (with all 3 stimulus conditions presented in random order), and participants completed between 8 and 11 blocks (with the vast majority completing 10 blocks). In order to minimize excessive movement artifacts, participants were told to focus their eyes on a central fixation cross during all conditions.

**EEG Acquisition.** Continuous EEG was recorded from 70 scalp electrodes at a digitization rate of 512 Hz using the BioSemi ActiveTwo™ electrode system with an open pass-band from DC to 150 Hz. The continuous EEG was recorded referenced to a Common Mode Sense (CMS) active electrode and a Driven Right Leg (DRL) passive electrode. CMS and DRL, which replace the ground electrodes used in conventional systems, form a feedback loop, thus rendering them references (for a description of the BioSemi active electrode system referencing and grounding conventions, visit www.biosemi.com/faq/cms&drl.htm).

**Behavioral Analyses.** Button press responses to the 3 stimulus conditions were acquired during the recording of the electroencephalography (EEG) and were processed offline using Matlab. RT means and standard deviations were calculated for each condition for each participant. Only trials with RTs falling within 2 standard deviations of an individual's average RT were considered valid. Thus, the range of RTs accepted was determined at the individual participant level. Given the large age range and the inclusion of a clinical population, significant inter-subject variability in RT was expected. Using a 95% cutoff to define the time window for acceptable trials rather than an absolute cutoff value allowed us to more accurately capture the range of RTs for each participant, an important factor in calculating the race model (described below). Hit rates, defined as the percent of trials on which a button press occurred within the
individual's specific RT range, were calculated for each participant. Slow responses, i.e., RTs more than 2.5 standard deviations below that individual's mean RT, were considered misses. A 2X2X3 mixed design ANOVA (with factors of Diagnostic Group, Age Group, and Stimulus Condition) was performed to assess group differences in hit rates.

To compare RTs across the 3 stimulus conditions and to assess group differences, a 3-way mixed design ANOVA (factors as above) was conducted. Planned comparisons between each of the unisensory conditions and the multisensory condition tested for the presence of the 'redundant signal effect' (RSE); that is, a faster reaction to multisensory than to unisensory stimuli, which in this case indicates behavioral facilitation for the multisensory condition compared to each of the unisensory conditions.

However, such facilitation may occur simply due to probability summation; therefore the more stringent criteria of Miller’s race model (Miller, J., 1982) was implemented. According to the race model, mean RTs decrease because there are now two inputs (e.g., auditory and visual) to trigger a response, and the fastest input wins. In this model, facilitation can be explained in the absence of interaction between the two inputs due to probability summation. However, when there is violation of the race model, it can be assumed that the unisensory inputs interacted during processing to facilitate RT performance.

**Testing the Race Model.** Miller’s (Miller, J., 1982) model places an upper limit on the cumulative probability (CP) of a response at a given latency for redundant signals (i.e., the multisensory condition). For any latency, t, the race model holds when this CP value is less than or equal to the sum of the CP from each of the single target stimulus conditions (the unisensory stimuli). For each individual, the range of valid RTs was calculated for the three stimulus types (auditory-alone, visual-alone, and audiovisual) and divided into quantiles from the 5th to 100th
percentile in 5% increments (5, 10, . . . , 95, 100%). Violations were expected to occur at
t quantiles representing the shorter RTs because this is when it was most likely that interactions of
the visual and auditory inputs would result in the fulfillment of a response criterion before either
source alone satisfied the same criterion (Miller, J., 1982; Ulrich, Miller, & Schroter, 2007). It is
important to note that failure to violate the race model is not evidence that the two information
sources did not interact, but rather it places an upper boundary on RT facilitation that can be
accounted for by probability summation.

At the individual level, a participant was said to have shown race model violation if the
cumulative probability of his/her RT to the AV stimulus was larger than that predicted by the
race model (see above) at any quantile within the first third of the distribution (represented by the
first 7 quantiles, i.e., the quantiles containing the lower end of RTs where violations are
expected to occur).

A 'Miller Inequality' value is calculated by subtracting the value predicted by the race
model from this cumulative probability value, and positive values represent the presence and
amount of race model violation. Figure 1 depicts unisensory, multisensory, and race model
values derived from the grand mean from all participants (N=118) to help the reader visualize
how these measures relate to one another. A secondary level of analysis was conducted at the
group level. For each of the four subject groups (TD: 7-10 years, TD: 11-16 years, ASD: 7-10
years, ASD: 11-16 years), Miller Inequality values (from each individual at each quantile
considered) were submitted to a t-test. The group was said to violate the race model at quantiles
in which the t-test was significant and the Miller Inequality value was positive. A less
conservative approach was also undertaken in which a 2 X 2 ANOVA directly tested for between
group differences in race model violation as indexed by maximum Miller Inequality value over the first third of the RT distribution.

Figure 1. Testing the race model. Mean data across the full dataset are presented (N=118). a) Reaction times and standard errors for the multisensory (AV) and unisensory conditions. b) Cumulative probability distributions for the multisensory (red trace), auditory-alone (blue trace), visual-alone (green trace) stimulus conditions, and the cumulative probability predicted by the race model (black trace). When the cumulative probability for the multisensory condition is greater than that predicted by the race model, race model violation has occurred. c) Miller Inequality: values greater than zero signify race model violation. Miller inequality values at the first seven quantiles (equivalent to the 35th percentile) were submitted to t-tests. Asterisks (*) indicate statistically significant race model violation.
EEG/ERP Processing and Analyses. Matlab was used for offline processing and analyses. A low-pass filter of 45 Hz with a slope of 24 db/octave, and a high-pass filter of 1.6 Hz with a slope of 12 db/octave were applied to each participant's continuous EEG. To generate ERPs the EEG was divided into 600 ms epochs (100 ms pre-stimulus to 500 ms post-stimulus onset) with baseline defined as -50 to +10 ms relative to stimulus onset. Trials that did not meet criteria for inclusion in the behavioral analyses (described above) were also excluded from the ERP analysis. Electrode channels with amplitudes larger than ±120 µV during the epoch surrounding stimulus presentation were considered to have excessive electromuscular activity, including those resulting from large eye-movements, and were interpolated on a trial by trial basis using the nearest neighbor spline (Perrin, Pernier, Bertrand, & Echallier, 1989; Perrin, Pernier, Bertrand, Giard, & Echallier, 1987). Channels with a standard deviation of less than 0.5µV across the block were interpolated on a block by block basis. Finally, if there were more than 4 bad channels in a trial, that trial was rejected (i.e., no more than 4 channels were interpolated for any given trial). Epochs were sorted according to stimulus condition and averaged for each participant. The resulting ERPs were re-referenced to an average of all electrodes. For each participant, the 'sum' condition was created by summing the ERPs from the auditory-alone and the visual-alone conditions. Group-averaged ERPs for all conditions were imported into Brain Electric Source Analysis (BESA) software for the purpose of visualizing the topographical distribution on the scalp.

An analysis of the unisensory responses was conducted to assess whether there were between-group differences in the componentry of the auditory-alone and visual-alone responses. The peak amplitudes of the auditory P1, N1a, N1b, N1c, and P2, and of the visual P1, and N1 were subjected to a multivariate ANOVA with Diagnostic Group (TD and ASD) and Age Group
(young and old) as the between group factors. The latency and electrodes used in the ANOVA were determined based on the grand averaged data for all participants (N=116).

AV interactions were measured by comparing the ERPs to the 'audiovisual' and the 'sum' conditions. This commonly used measure of multisensory processing (e.g., Brandwein et al., 2011; Foxe et al., 2000; Giard & Peronnet, 1999; Molholm et al., 2002; Murray, M. M., Molholm, et al., 2005; Russo et al., 2010; Teder-Salejarvi, W. A. et al., 2002) is based on the principle of superposition of electrical fields, and relies on nonlinear summation as evidence for multisensory interactions (e.g., that the auditory and visual inputs interacted). A benefit of using this measure, particularly when conducting between groups comparisons, as in the present study, is that MSI is always calculated relative to the individual's unisensory processing. This repeated measures design provides a built in control for between subject differences in unisensory processing.

For the primary statistical analyses of the multisensory effects, mixed-design ANOVAs with factors of Diagnostic Group (TD and ASD), Age Group (7-10 year and 11-16 year age groups), and Condition ('AV' and 'sum') were used. The latency and regions included in the planned analyses were based on findings from previous work (Brandwein et al., 2011) which showed AV MSI in healthy children at 100-120 ms over fronto-central scalp and between 180-210 over left and right parieto-occipital areas (roughly corresponding to the visual N1). When appropriate, the results of the ANOVAs were based on Greenhouse–Geisser corrections, and significant effects were followed by post-hoc comparisons with Bonferroni adjustments.

A second level of analysis was employed to more fully describe the multisensory data. This relatively unconstrained approach allows a snapshot view of effects across the full dataset and serves as an important hypothesis generation tool for future studies. So-called Statistical
Cluster Plots (SCPs) were created by plotting the results of running $t$-tests comparing the 'AV' and 'sum' ERPs at each time point, for each electrode. The probability of Type-1 errors was decreased by only considering those data points that reached significance (at the $p \leq 0.05$ level) for at least 10 subsequent consecutive time points (which, given the 512 Hz. digitization rate, would exclude effects that did not last for at least 19.5 ms) and at three or more adjacent electrodes sites. Further explanation of this approach can be found elsewhere (e.g., Brandwein et al., 2011; Guthrie & Buchwald, 1991; Molholm et al., 2002; Russo et al., 2010). Cluster plots of the 'AV' compared to the 'sum' ERP data were generated for each of the 4 participant groups.

**Topographical Analysis.** To assess differences in the underlying neural generator configuration responsible for observed multisensory effects across groups, we used the Topographical ANOVA (TANOVA), as implemented in the Cartool software (http://sites.google.com/site/fbmlab/cartool), comparing MSI between TD and ASD groups using global dissimilarity and non-parametric randomized testing for each age group. Global dissimilarity is an index of configuration differences between two scalp distributions, independent of their strength. For each subject and time point, a single value is generated, which varies between 0 and 2 (0, homogeneity; 2, inversion of topography). To create an empiric probability distribution against which the global dissimilarity can be tested for statistical significance, the Monte Carlo MANOVA was applied (for a more detailed description see Manly, 1991). To control for Type I errors, a period of statistical significance was only considered significant if an alpha criterion of 0.05 or less was obtained for at least 11 consecutive sample points (~21ms) (Butler et al., 2011; Foxe & Simpson, 2002; Guthrie & Buchwald, 1991).
**Correlation Analysis.** To explore the relationship between neural and behavioral measures of AV integration, a partial correlation coefficient was computed for race model violation (e.g., the largest Miller Inequality value for each participant over the first third of the RT distribution) and the difference between the AV and the sum ERP between 100-120 ms over frontocentral scalp, controlling for age of the participant. This latency and region were chosen *a priori* based on significant MSI effects in previous studies of TD children (Brandwein et al., 2011).

**Results**

**Behavioral measures of multisensory integration (MSI)**

Participants performed a simple RT task, responding with a button press to randomly presented auditory stimuli (a tone), visual stimuli (a red disc against a black background), and multisensory stimuli (both stimuli presented simultaneously). As detailed in Table 2, although all children performed well, children in the TD group had a higher hit rate than those in the ASD group \((F(1,114)=12.254, p<0.01)\) and the older participants had higher hit rates than the younger participants \((F(1, 114)= 9.414, p<0.01)\). Within groups hit rate was highest for the AV condition and lowest for the visual condition \((F(1.536,175.134)= 60.058, p<0.01)\). Mean RTs (Table 2) for all stimulus conditions were significantly faster in TD children than in the children with ASD \((F(1,114)=7.542, p<0.01)\), and in the older group compared to the younger group of children \((F(1,114)=10.813, p<0.01)\). While the TD children showed greater quickening of RTs as a function of age compared to the children with ASD, there was no significant interaction of Age Group and Diagnostic Group. For all groups, RTs to multisensory stimuli were significantly faster than to either the auditory or the visual stimuli \((F(1.692, 192.901)= 254.668, p<0.01)\),
indicating the presence of a Redundant Signal Effect (RSE). Neither Diagnostic Group nor Age Group interacted with stimulus condition indicating similar patterns of RSE for all groups.

Table 2.

<table>
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<tr>
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<th>Younger children: 7–10 years</th>
<th>Older children: 11–16 years</th>
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<tbody>
<tr>
<td></td>
<td>TD</td>
<td>ASD</td>
</tr>
<tr>
<td>Hit rate (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory</td>
<td>90 (4)</td>
<td>87 (6)</td>
</tr>
<tr>
<td>Visual</td>
<td>88 (6)</td>
<td>84 (8)</td>
</tr>
<tr>
<td>AV</td>
<td>91 (4)</td>
<td>88 (5)</td>
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<tr>
<td>RT (ms)</td>
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<td></td>
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<tr>
<td>Auditory</td>
<td>463 (109)</td>
<td>498 (142)</td>
</tr>
<tr>
<td>Visual</td>
<td>473 (113)</td>
<td>507 (133)</td>
</tr>
<tr>
<td>AV</td>
<td>410 (109)</td>
<td>449 (127)</td>
</tr>
</tbody>
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Refer to the main text for a description of the statistically significant differences between conditions and groups.

**Results of race model analysis.** To determine whether quickening of responses to the multisensory condition exceeded the amount predicted by the statistical summation of the fastest unisensory responses (see methods), the RTs of all participants were subjected to a race model analysis. In the 7-10 year old groups, 73% of the children with TD and 55% of the children with ASD showed some violation of the race model in at least one of the first 7 quantiles. In the 11-16 year old groups, more children showed violation: 95% in the TD group and 71% in the ASD group. Figure 2 illustrates, at a quantile-by-quantile level, the percentage of individuals in each group that violate the race model across the first third of the RT distribution.
Figure 2. The percentage of children in each group who show violation of the race model at each of the 7 quantiles considered (the first third of the reaction time distribution). TD = children with typical development, ASD = children with autism spectrum disorders.

To test the reliability of race model violations at the group level, for each of the 7 quantiles considered, Miller Inequality values were submitted to $t$-tests. As illustrated in Figure 3, neither of the ASD groups showed significant race model violation. In contrast, both TD groups showed significant race model violation; the younger TD group violated in the first two quantiles, and the older TD group across all tested quantiles (similar to findings from our earlier
investigation, Brandwein et al., 2011). Overall, the older ASD group showed much less race model violation than the older TD group, as indicated by lower Miller Inequality values. Descriptively, the older ASD group showed a pattern of race model violation that was more similar to that of the younger TD group. Though the magnitude and duration of race model violation appeared somewhat similar in the young TD group and the old ASD group, it is important to note that the old ASD group did not show significant race model violation while the young TD group did.

To statistically compare race-model violation between groups, a second approach to analyzing race-model violation evaluated the relationship of Diagnostic Group and Age Group on race-model violation. The ANOVA revealed that the magnitude of race model violation, as indexed by the maximum Miller inequality value in the first third of the RT distribution, was significantly larger in the TD group than in the ASD group \((F(1,114)=19.732, p<0.01)\), and in the older age group compared to the younger age group \((F(1,114)=19.996, p<0.01)\). Furthermore, a significant interaction \((F(1,114)=5.174, p<0.05)\) indicated that age has an effect on maximum race model violation in the TD group (with the magnitude of violation being greater in the older than in the younger group), but that age did not have a significant effect in the ASD group.
Figure 3. Miller Inequality curves are presented for each of the four groups. Values greater than zero signify race model violation. Miller inequality values at the first seven quantiles (equivalent to the 35th percentile) were submitted to t-tests. Asterisks (*) indicate statistically significant race model violation.
**Unisensory ERPs**

**Auditory Evoked Potentials (AEPs).** The expected developmental changes in the morphology of the auditory P1-N1-P2 complex were observed for both ASD and TD groups (Figure 4). Consistent with previous findings in healthy children (Brandwein et al., 2011; Ceponiene et al., 2002; Gomes et al., 2001; Ponton et al., 2000), the frontocentrally focused P1 appeared earlier and smaller in the older groups of children, the frontocentrally focused auditory N1 (or N1b) was earlier and more prominent in the older groups of children (with a polarity reversal at temporal sites), and the lateral components of the N1 (the N1a and N1c) were more negative in the younger groups of children. While the general morphology of the auditory ERPs was similar in the TD and ASD groups, there were some specific group differences, particularly between the younger age groups, with the ASD group having a larger lateral N1a and a smaller lateral N1c. The results of a multivariate ANOVA confirmed a main effect of age on amplitude for the auditory P1 ($F(1,112)=15.683, p<0.01$), N1a ($F(1,112)=10.563, p<0.01$), N1b ($F(1,112)=12.896, p<0.01$), and N1c ($F(1,112)=11.001, p<0.01$). A main effect of Diagnostic Group confirmed that the peak amplitude of the N1c was smaller in the ASD compared to the TD children $F(1,112)=4.882, p<0.05$). In contrast, the amplitudes of the auditory P1, N1a, and N1b were not significantly different between the TD and ASD groups, and there were no significant interactions of Age Group and Diagnostic Group on the amplitude of any of the auditory components considered.
Figure 4 Auditory ERPs. Mean ERPs to the auditory-alone condition are presented for each of the four groups. Traces represent the composite signal from two adjacent electrodes, the locations of which are indicated on the head models.

Visual Evoked Potentials (VEPs). The visual-alone ERPs also showed the expected morphology for both the TD and ASD groups, characterized by an occipitally focused P1, and an N1 over bilateral lateral occipital scalp areas (Figure 5). The most apparent group difference was that the P1 and N1 were of much larger amplitude in the younger compared to the older children, which is consistent with prior reports that the amplitudes of the visual P1 and N1 decrease across development (Brandwein et al., 2011; Hileman, Henderson, Mundy, Newell, & Jaime, 2011; Hirai, Watanabe, Honda, & Kakigi, 2009; Kuefner, de Heering, Jacques, Palmero-Soler, & Rossion, 2010; Lippe, Roy, et al., 2007). The peak of the visual N1 appeared broader and later in the ASD compared to the TD groups. A multivariate ANOVA confirmed a main effect of Age.
Group on amplitude for the visual P1 only \( (F(1,112)=35.814, p<0.01) \). The visual N1 was significantly more negative in the participants with TD compared to those with ASD \( (F(1,114)=11.200, p<0.01) \). The amplitude of the visual P1 was similar in the TD and ASD groups, and there were no significant interactions of Age Group and Diagnostic Group on the amplitude of the visual P1 or N1.

![Figure 5. Visual ERPs. Mean ERPs to the visual-alone condition are presented for each of the four groups. Traces represent the composite signal from two adjacent electrodes, the locations of which are indicated on the head models.](image)

**Neural measures of multisensory integration (MSI)**

AV interactions, as indicated by differences between the multisensory and the summed ERPs, were readily observable between 100-120 ms over fronto-central scalp in the two TD groups (Figure 6a) but not in the ASD groups. In the TD groups the multisensory response was more negative in amplitude than the summed response. An ANOVA confirmed a main effect of Condition \( (F(1, 112)=9.078, p<0.01) \) and more pertinent to our hypothesis, a significant
interaction of Diagnostic Group and Condition \( (F(1, 112)=7.528, p<0.01) \). Age Group did not have a significant effect on Condition. At the second latency and region of interest, 180-210 ms over left and right parietal-occipital areas, both the TD and the ASD groups showed AV interactions. A main effect of Condition \( (F(1, 112)=4.702, p<0.05) \) confirmed that the multisensory response in this latency and region was significantly more negative going than the summed response. There were no significant interactions of Diagnostic Group and/or Age Group with Condition.

**Exploratory Statistical Cluster Plots (SCPs).** To further characterize the spatiotemporal characteristics of AV integration in each of the groups, SCPs representing significant results of running \( t \)-tests between the multisensory and sum conditions for all electrodes at all time points (between 50 ms pre-stimulus onset to 300 ms post-stimulus onset) were generated for each group (see Methods). The cluster plot analysis (Figure 7) revealed early interactions of auditory and visual processes in the oldest TD group between 40-80 ms over left parieto-occipital and frontal scalp regions. AV interactions were seen in all four groups between 100-130 ms over parietal scalp. In the older TD group, AV interactions in this time frame were widespread, also appearing over frontal, fronto-central, and occipital scalp. The next clear AV interactions were centered around 150 ms over multiple regions in both young and old TD groups, but not in the ASD groups. Widespread AV interactions from 275 ms onwards can be seen in the SCPs for all four groups and are not discussed further as they most likely represent cortical activity related to motor responses (which occurs in response to all stimuli and is thus represented twice in the sum response).
Figure 6. Multisensory effects at 110 ms. a) Multisensory (AV) and summed (A+V) ERPs and their difference (AV-(A+V)) are shown for each of the four participant groups. Traces represent the composite of four adjacent fronto-central electrode sites (Fz, FCz, FC1, and FC2). Gray bars highlight the 100-120 ms window of analysis. b) Voltage maps depict the scalp distribution of the MSI effect at 110 ms poststimulus onset (the difference between the multisensory and summed responses). c) Multisensory (AV) and summed (A+V) ERPs and their difference (AV-(A+V)) are shown for each of the four participant groups. Traces represent the composite of four adjacent parietal electrode sites (Pz, P1, P2, CPz). d) Results of the TANOVA analysis. Significant topographical differences between the TD and ASD groups are marked in red, presented separately for young and old age groups.
Figure 7. Statistical Cluster Plots: running t-tests comparing the multisensory and sum ERPs for each of the 4 groups. Significance is depicted for effects meeting a 0.05 alpha criterion and lasting for at least 10 consecutive data points (19.2 ms at 512 Hz sampling rate). The color bar indicates directionality of the effects, with white indicating an absence of significant t values. Time is plotted on the x-axis from -50 to 300 ms. Electrodes are plotted on the y-axis. Starting from the bottom of the graph, the electrodes are divided into sections from posterior to anterior scalp with each color representing 4-5 electrodes, the relative positions of which are located on the corresponding head.
Topographical Analysis. A TANOVA analysis revealed no differences in the topographies of the young TD and ASD groups (Figure 6d), a finding that could be the result of relatively small MSI effects in both groups. There were differences between the older TD and ASD groups that onset at about 90-128 ms, and corresponded with readily observable differences in topography of MSI in that timeframe (see Figure 6d).

Post-hoc ANOVAs. Based on findings from the SCP running t-test analysis (Figure 7), three additional ANOVAs were conducted to assess group differences in MSI: over left parieto-occipital scalp between 40-80 ms, over parietal scalp between 100-130 ms, and over parieto-occipital scalp between 140-160 ms. For the earliest time period there were no effects or interactions involving Condition. In the next timeframe, consistent with the SCPs, a main effect of Condition was observed ($F(1,112)=42.774, p<0.01$) over parietal scalp in the 100-130 ms timeframe, with the summed response appearing more negative than the multisensory response (Figure 6c). There were no group differences in MSI between 100-130 ms over parietal regions. Between 140-160 ms a main effect of Condition ($F(1, 112)=12.458, p<0.01$) over posterior scalp indicated that the multisensory response was significantly larger than the summed response. As illustrated in Figure 8, this effect was qualified by a significant interaction between Condition and Diagnostic Group ($F(1,112)=7.814, p<0.01$) such that AV interactions were larger in the TD groups compared to the ASD groups. There were no effects involving Age Group.
Figure 8. MSI effects at 150 ms. Multisensory (AV) and summed (A+V) ERPs and their difference (AV-(A+V)) are shown for each of the four participant groups. Traces represent the composite of three adjacent left parieto-occipital sites (PO7, PO3, O1; location indicated with a dashed circle on the left most voltage map). Gray bars highlight the 140-160 ms window of analysis. Voltage maps depict the scalp distribution of the MSI effect (the difference between the multisensory and sum responses) at 150 ms.

Correlations between neural and behavioral measures of multisensory integration

A partial correlation, controlling for age, revealed a relationship between maximum race model violation and neural measures of AV integration over fronto-central scalp between 100-120 ms that trended toward significance ($r_{116}=-.174$, $p=0.06$). An additional post-hoc partial correlation analysis, also controlling for age of the participant, was conducted in the 140-160 ms timeframe over parieto-occipital scalp where TD children show robust AV neural interactions. A significant correlation ($r_{116}=.305$, $p<0.01$) confirmed that maximum race model violation is correlated with neural measures of AV integration over parieto-occipital scalp between 140-160 ms. Considering the TD and ASD children separately indicated that this correlation was only significant in the TD children ($r_{71}=.256$, $p<0.05$).
Discussion

Research in autism has been heavily weighted towards developing and testing theoretical frameworks within which the core features of the disorder - impairments in social interactions and communication, and stereotyped, rigid patterns of behavior, may be better understood (see Baron-Cohen, Richler, Bisarya, Gurunathan, & Wheelwright, 2003; Hill & Frith, 2003; Ozonoff et al., 1991; Schultz et al., 2003 for discussions and reviews of executive function, theory of mind, weak central coherence, empathizing and systemizing, and social cognition theories of ASD). Sensory atypicalities frequently observed in this population are largely conceptualized as secondary to the core symptoms of autism (Rogers & Ozonoff, 2005). Despite renewed discussion of sensory integration deficits in ASD and their impact on cognition, to date only a few studies have investigated whether basic multisensory integration (MSI) is intact in ASD, and these studies have yielded mixed and often contradictory results. The present study applied well-characterized metrics of MSI to describe multisensory processing for basic AV stimuli in a large sample of children and adolescents with and without a diagnosis of ASD. The resulting electrophysiological and behavioral data revealed striking differences between individuals with and without ASD, both in terms of the neural processes involved in integrating simple AV stimuli, and in terms of ensuing behavioral consequences.

Behavioral findings

Multisensory processing was measured behaviorally using a simple audiovisual (AV) reaction time (RT) task, for which it has been shown that multisensory facilitation of performance and the associated neural processes develop gradually over middle childhood, reaching adult-like levels by about 14 years of age (Brandwein et al., 2011). The present findings replicated this result in the TD group. Not only was multisensory facilitation of
behavior present in both younger and older TD groups, but it was significantly greater in the older group. In stark contrast to the TD group, neither the younger nor the older children with ASD showed significant multisensory facilitation of behavior at the group level.

**Electrophysiological findings**

Paralleling these behavioral differences, children with ASD showed diminished and less widespread cortical AV interactions compared to the TD group. Reduced neural integration in the ASD groups was seen as early as 100 ms after stimulus onset over fronto-central scalp (see Figure 6a and 6b), an area/timeframe of MSI that both the current and prior research indicates is associated with behavioral benefits (multisensory facilitation of RTs) in TD children (Brandwein et al., 2011). What is more, for the older groups of participants, statistical analysis confirmed different topographical distributions for MSI (Figure 6d), which indicates differences in the cortical circuitry that underlies the scalp recorded MSI effects. Following this initial stage of AV integration (at around 100 ms) was a period, onsetting around 150 ms, where TD groups exhibited clear and robust widespread AV interactions (Figures 7 and 8) that were absent in ASD groups. Thus it appears that the integration of basic AV information in children with ASD involves reduced neural activity, particularly over frontal and parieto-occipital scalp areas. Considered along with our behavioral findings, the electrophysiological results indicate that the neural networks that underlie MSI in ASD are not as effective as those engaged in TD children.

A somewhat unexpected finding was that robust MSI was observed in the ASD group already by ~100 ms post-stimulus (Figure 7), on par with the onset of the major MSI effect in the TD group. In contrast, Russo and colleagues (2010) found that auditory-somatosensory MSI of basic stimuli was essentially completely absent in ASD children until about 310 ms, whereas the TD group showed MSI effects by about 100 ms. This across-study difference could reflect the different
sensory modalities involved, or it could be related to differences in how attention was allocated. In the auditory-somatosensory study, which showed absence of early (circa 100 ms) MSI in the ASD group, participants were instructed to ignore the stimuli and watch an unrelated movie. In contrast, in the current study, participants were required to attend and make a response to the eliciting stimuli. Thus, it is possible that individuals with ASD need to actively attend stimuli in order for relatively early MSI to occur, whereas this is not the case for individuals with TD.

Consistent with this notion, evidence from an auditory mismatch negativity study highlights this idea that impaired automatic processing in children with ASD can be normalized through the investment of attention (Dunn, M., Gomes, & Gravel, 2008). Indeed, given that there were small but significant performance differences between our ASD and TD groups, we cannot rule out that cognitive factors such as attention may have contributed to the observed differences in multisensory processing. The precise role of attention in the invocation of multisensory processing is currently a matter of significant research interest (e.g., Molholm, Martinez, Shpaner, & Foxe, 2007; Senkowski, Saint-Amour, Gruber, & Foxe, 2008; Talsma, D., Doty, & Woldorff, 2007; Zimmer, U., Itthipanyanan, Grent-'t-Jong, & Woldorff, 2010), and clearly the role of attention and its impact on multisensory processing in ASD needs to be directly tested using a design that explicitly manipulates attention.

**Evidence for Disordered Connectivity?**

Reduced MSI in individuals with ASD is consistent with the *disrupted connectivity* theory of autism that has been receiving considerable attention of late. While several variations exist, these theories refer to the general hypothesis that the short and long-distance connections between cortical regions are compromised in autism, and that reduced functioning of this neural circuitry results in impaired integration of information at the neural, cognitive, and social levels.
(Just et al., 2004; Wass, 2011). These models are based in part on findings from 'functional connectivity MRI', or fcMRI, studies that indicate abnormal communication between functional cortical networks and regions in autism (Muller et al., 2011). For example, individuals with ASD show reduced synchronization between frontal and parietal areas while performing an executive functioning task (Just et al., 2007), between cortical language systems during a sentence comprehension task (Just et al., 2004), and between the fusiform face area and frontal areas during a working memory task involving face processing (Koshino et al., 2008).

Anatomical evidence for diminished long-distance connectivity in autism includes findings of reduced integrity of the callosal fibers connecting sensory cortices and prefrontal areas (Barnea-Goraly et al., 2004), of atypical developmental trajectories for cerebral white matter volume (see Courchesne & Pierce, 2005a for a review), and from post-mortem studies showing abnormal microcircuitry of minicolumns (Buxhoeveden et al., 2006; Casanova, Buxhoeveden, Switala, & Roy, 2002) which may alter local as well as long-range cortical connections (reviewed in Courchesne & Pierce, 2005a; Courchesne et al., 2005). Though the present study cannot assess whether neural under-connectivity plays a causal role in the observed behavioral impairments in MSI, a significant correlation between our neurophysiological and behavioral measures of MSI is consistent with the notion that impaired long-range cortical connectivity between spatially remote primary auditory and visual cortices, could lead to deficient integration of simple AV information.

**Very early MSI effects**

Also unexpected was the finding from an exploratory analyses of a period of very early AV integration (onsetting at about 40 ms) over parieto-occipital scalp, that was exclusive to the older TD group (Figure 7). We and others have observed a similar period of early stage AV MSI
in adults (e.g., Giard & Peronnet, 1999; Molholm et al., 2002), but had not specifically designed the current study to be sensitive to such early modulation (see Molholm et al., 2002), and had failed to observe the same in our recent developmental study (Brandwein et al., 2011). We are cautious about drawing strong conclusions from this finding, especially because a between groups analysis of this very early effect did not reach significance. However, one possibility is that the cortical connections that contribute to very early MSI develop over childhood and are not yet stable in adolescence. A study powered to test this hypothesis and specifically designed to be sensitive to early modulations is needed.

**Developmental course of MSI in ASD**

By directly comparing data from older and younger groups, we were able to track the developmental course of basic AV processing in ASD. This is particularly important given that ASD is characterized by delays in specific developmental milestones and atypical developmental trajectories. The developmental nature of ASD with respect to AV integration is highlighted by preliminary findings from our laboratory using an AV speech-in-noise paradigm (Foxe et al., 2009), and findings from another study by Taylor and colleagues (2010), both of which indicate that children with ASD 'catch up' to their same-aged peers on AV MSI in their teenage years, at least when it involves AV speech. In contrast, the current data suggest that integration of simple AV stimuli is fundamentally different, not developmentally delayed or simply immature in ASD. Moreover, the lack of significant race model violation in the children with ASD suggests that in addition to being different, the neural processes involved in integrating the AV information are less efficient than in children with TD.
Conclusions

Findings from the current study provide evidence that children with ASD integrate even very basic, non-social AV stimuli differently and less effectively than children with TD. Neural indices of MSI indicate that children with ASD rely on different cortical regions at a relatively early stage of information processing, as shown by topographical analysis (Figure 6d). These findings strongly point to a general deficit in AV integration that is independent of social or high-order cognitive deficits. While it is unlikely that impairments in basic MSI, such as those demonstrated here, can account for the entire constellation of symptoms observed in ASD, both could result from common underlying differences in connectivity and it is not difficult to see how disruptions in fundamental integration of basic sensory information might contribute to social and communicative deficits characteristic of individuals with ASD. For example, suboptimal integration of AV inputs may make it more difficult for young children to benefit from the redundant visual-articulatory information that supports language learning independent of any biases compromising the processing of “social” stimuli. Atypical connections between sensory cortices and more anterior and integrative brain areas may disrupt the formation of meaningful relationships between congruent auditory and visual inputs. That said, it is possible that more ecologically valid stimuli and/or a more challenging task than the one employed here might bring out 'work-around' strategies in the children with autism that allow them to compensate for these early impairments in automatic multisensory processing. Though highly speculative, it may be that for important functions such as speech recognition, compensatory processes involving frontal lobe development (e.g., improvements in executive function) contribute to the 'catching up' observed in some behavioral studies of AV integration in ASD over childhood (Foxe et al., 2009; Taylor et al., 2010).
CHAPTER 3

Predicting Autistic Symptom Severity and Sensory Sensitivities from Neurophysiological and Behavioral Indices of Early Sensory Processing and Integration
Abstract

Atypical processing and integration of sensory inputs are commonly hypothesized to play a significant role in the unusual sensory reactions and social-cognitive deficits of individuals with autism spectrum disorders (ASD). Specific reports on the relationship between objective metrics of sensory processing and clinical symptoms, however, are surprisingly sparse. Here we sought to relate experimental findings to the readily observable symptoms of ASD, examining the relationship between neurophysiological assays of early stage sensory processing and two clinical variables, severity of autism symptoms and sensory sensitivities. Participants were children and adolescents with ASD aged 7-16 years. Linear regression analysis revealed significant associations between neural markers of sensory processing (reflecting auditory processing and audiovisual integration) and severity of autistic symptoms, as indexed by the Autism Diagnostic Observational Schedule. In contrast, there were no significant relationships between these electrophysiological measures and parent-reported visual/auditory sensitivities from the Short Sensory Profile. These results provide compelling evidence that sensory-level cortical processing atypicalities are related to core symptoms of autism. These data further the case for the use of neurophysiological measures of brain activity as endophenotypic markers of key features of the autism subphenotype.
Introduction

The last decade has seen a surge in research aimed at identifying neurophysiological and neuroanatomical abnormalities associated with autism spectrum disorders (ASD). Though a tremendous amount of data have been collected and analyzed, the underlying neuropathology of ASD remains elusive. Progress has been limited, in part due to methodological issues (inconsistent findings, variability in study design and participant characteristics, and difficulties integrating results across studies and disciplines), but also because of the inherent complexity of this disorder. An important step in gaining understanding, therefore, is to relate experimental findings to the readily observable symptoms of ASD. In light of this challenge, the current study examines the clinical significance of the findings presented in Chapter 2 (i.e., Brandwein et al., 2013) by asking whether our established neurophysiological correlates of sensory processing and integration predict the severity of core and associated symptoms of autism. The strength of this approach is its potential for identifying endophenotypes within this heterogeneous disorder, which may then serve as biological markers. The importance of developing such biomarkers cannot be overstated given their potential for early identification and sub-classification of individuals with ASD. Such classification in turn will allow application of specific therapies targeted at treating subgroups of individuals who, because of a similar pathophysiology, are more likely to respond to a particular intervention.

A central challenge to translating research findings from 'bench-to-bedside' is that ASD is unusually diverse with respect to the range and severity of symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association, 2000), for an individual to be diagnosed with an ASD there needs to be a qualitative impairment in social interaction and in communication, and evidence of restricted, repetitive and
stereotyped patterns of behavior, interests, or activities. While social-communication impairments and behavioral rigidity are, by definition, present in all individuals diagnosed with autism, there is tremendous clinical variability in the manifestation and expression of these symptoms (Jones & Klin, 2009). The poor specificity of the DSM-IV criteria for ASD (Grzadzinski, Huerta, & Lord, 2013; Huerta, Bishop, Duncan, Hus, & Lord, 2012) may be an important contributing factor to heterogeneity in this population. Additional factors that are not captured in the DSM-IV; particularly, the varying levels of symptom severity, the degree of functional impairment, and the presence of associated symptoms (e.g., sensory symptoms), add to the complex and varied clinical presentation. While the recently published DSM-5 (American Psychiatric Association, 2013) improves on some of these issues (discussed later), these revised diagnostic criteria have not yet been incorporated into translational research design.

A common approach in autism research is to examine groups of individuals with a specific ASD diagnosis; i.e., Autistic Disorder, Asperger’s Disorder, or Pervasive Disorder-NOS, and/or to look at between group differences in these diagnostic categories. Defining groups (or limiting samples) based on a diagnostic category has the potential to be useful in identifying possible markers of etiology if the validity of the diagnostic categories is well-established. However, the majority of research calls into question the validity of Asperger's Disorder as a unique disorder distinct from Autistic Disorder (Macintosh & Dissanayake, 2004; Mayes & Calhoun, 2001; Miller, J. N. & Ozonoff, 2000; Witwer & Lecavalier, 2008). Furthermore, research has documented that the majority of those individuals who at some point received a clinical diagnosis of Asperger’s Disorder did not actually meet DSM-IV criteria for this specific diagnosis (Mayes, Calhoun, & Crites, 2001; Szatmari, Archer, Fisman, Streiner, & Wilson, 1995). Even when standardized diagnostic instruments were used, clinical distinctions between
the three disorders have proven unreliable across sites (Lord et al., 2012). For these and other reasons, the DSM-5 has replaced the specific diagnostic subcategories (autism, Asperger’s, PDD-NOS) with a single all-encompassing category of autism spectrum disorder.

Cognitively, individuals with ASD present with a wide range of intellectual and language abilities. As such, limiting research samples to individuals of a particular cognitive level (e.g., IQ, mental age, language skills, etc.) is another method frequently used in autism research. Indeed, using a cognitively homogenous group of participants is particularly important when making between group comparisons of performance on cognitive tasks. Stratifying groups by intellectual or language level may also be of interest for sub-typing the disorder based on cognitive phenotypes. However, measures such as IQ and language do not directly reflect how "autistic" an individual or a group is.

An alternate approach to studying a disorder with such a heterogeneous clinical presentation is to stratify the groups by the 'severity' of their autistic presentation. That is, participants are characterized, or groups are defined, based on the severity of their core symptoms of autism, not their level of language, cognition, or DSM-IV diagnosis. The importance of characterizing symptom severity is recognized in the DSM-5 by the inclusion of severity specifiers. It is likely that the addition of these severity specifiers will assist clinicians to more adequately describe their patients. However, the utility of these new severity ratings, at least for research purposes, will depend upon whether autistic symptom severity can be systematically and reliably quantified.

‘Measuring' Autism

Until recently merely making a reliable diagnosis of ASD, let alone establishing the severity of the disorder, was a significant challenge. Fortunately the field has moved ahead to
improve on these measurement issues. Over the last two decades the Autism Diagnostic Observational Schedule (ADOS; Lord et al., 1999) has emerged as the gold standard for classifying an individual as being on the autism spectrum. The ADOS is a semi-structured observation of the individual designed to measure both the quantity and quality of the child's social-communication skills, as well as his/her stereotyped behaviors and restricted interests. The activities and questions on the ADOS provide opportunities to observe communication, social interactions, and responses to the environment. Though a developmental history of the individual is necessary for clarifying and confirming a diagnosis of ASD, ADOS scores are valuable because they reflect a professional's direct observation of the individual's current behavior, rather than depending solely on the parent’s report. Another feature of the ADOS that makes it a preferred tool for measuring symptoms associated with autism is that scores are relatively independent of the individual's language level, general cognitive level, and age. This is particularly important because the social-communication expectations for an individual with limited language (or of a younger age) are quite different from those of a fluent (or older) individual.

The ADOS provides raw scores that have recently been normalized to represent a severity index called the Calibrated Severity Scores or CSS (Gotham, Pickles, & Lord, 2009). The CSS are on a 10-point scale and provide a measure of autistic symptom severity in an individual, relative to others of a similar age and language level. Because these calibrated ADOS severity scores became available only in 2009, there are not yet any published studies examining how they might relate to neurophysiological findings in ASD, to our knowledge. This current study will use the CSS in assessing the relationship between neurophysiological markers and autism severity.
Measuring Sensory Symptoms in ASD

As detailed in the general introduction of this dissertation, unusual sensory responses and interests have been associated with autism since the disorder was first described in the 1940s. Sensory symptoms are a significant source of stress for individuals with ASD and their families. For example, sensory sensitivities and experiences were associated with atypical cortisol levels (Corbett, Schupp, Levine, & Mendoza, 2009) and stress levels (Gillott & Standen, 2007) in individuals with ASD. Families reported that their routines and activities were significantly affected by their child's sensory-related behaviors (Schaaf, Toth-Cohen, Johnson, Outten, & Benevides, 2011). As a group, parents ranked hyper-sensitivity as the third most concerning issue about their children (McConachie et al., 2013). A recent study suggests that sensory over-responsivity in toddlers with autism is associated with increased maternal stress and disruptions in family life (Ben-Sasson, Soto, Martinez-Pedraza, & Carter, 2013). While hyper-sensitivity and over-responsivity to stimuli appear to be the more problematic sensory related behaviors described, under-responsivity to stimuli is also frequently noted (see Ben-Sasson et al., 2009 for a meta-analysis).

Measuring the presence and severity of sensory symptoms in ASD, or in any population for that matter, has been a significant challenge for researchers. Whereas a standard measure exists for the systematic observation of autistic symptoms (i.e., the ADOS), there is no accepted standard observational measure of sensory symptoms. Currently the most widely used tool for measuring sensory atypicalities in children is the Short Sensory Profile (SSP; McIntosh et al., 1999). This 38-item questionnaire, which is derived from the more extensive Sensory Profile (Dunn, W., 1999), asks parents/caregivers to rate their child's reactions, preferences, and tendencies when confronted with everyday sensory stimuli and situations based on a 5-point
scale. The SSP provides an overall measure of sensory processing patterns as well as domain specific scores. In the current study, the 'visual/auditory sensitivity' domain score (VAS) is the independent or clinical outcome variable used to examine whether neurophysiological measures of auditory and visual sensory processing and integration can predict real-life auditory and visual sensitivities as reported by parents. The items that make up this section of the SSP are presented in Table 1.

**Table 1.** Parents/Caregivers rate how often their child exhibits each of these behaviors based on the following scale: (1) Always, (2) Frequently, (3) Occasionally, (4) Seldom, (5) Never

<table>
<thead>
<tr>
<th><strong>Visual/Auditory Sensitivity</strong></th>
<th><strong>(Short Sensory Profile; McIntosh et al., 1999)</strong></th>
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<tr>
<td>Responds negatively to unexpected or loud noises (for example, cries or hides at noise from vacuum cleaner, dog barking, hair dryer)</td>
<td></td>
</tr>
<tr>
<td>Holds hands over ears to protect ears from sound</td>
<td></td>
</tr>
<tr>
<td>Is bothered by bright lights after others have adapted to the light</td>
<td></td>
</tr>
<tr>
<td>Watches everyone when they move about the room</td>
<td></td>
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<tr>
<td>Covers eyes or squints to protect eyes from light</td>
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**Neurophysiological markers of sensory processing and integration**

As nearly everyone now agrees that autism is a brain-based disorder, a significant amount of research is directed at identifying the neurobiological underpinnings of ASD. There is a growing interest in understanding how the autistic brain processes and combines sensory information. The majority of studies that have investigated the neurophysiological basis of sensory processing and integration examined neural responses to social stimuli such as faces and speech. Given that autism is defined by the presence of social and communication impairments, it is not surprising that research has concentrated on the higher-order processing of language,
facial expressions, and emotion recognition. However, complex information processing is dependent, at least to some extent, on the integrity of low-level basic sensory processing. To this end, Chapter 2 of this volume characterized basic auditory and visual processing and audiovisual integration using objective metrics of sensory processing in the brain. Electrophysiological responses were recorded while children with ASD and those with typical development performed a simple audiovisual reaction time task. Taking developmental changes into consideration, Chapter 2 showed that early (<150 ms) event related potentials (ERPs) associated with sensory registration of auditory and visual stimuli (simple tones and red discs) were largely intact in children and adolescents with ASD. It remains to be seen whether or not variability of these early auditory and visual components reflects behavioral (symptom severity) differences within our ASD group. By parsing these data in terms of clinical symptomology we will explore whether our neural markers of auditory and visual processing bear any relationship with autistic and sensory symptom severity, as measured with standard clinical instruments.

Examining multisensory integration (MSI) offers an additional opportunity to understand how the brain deals with sensory inputs. As discussed in previous chapters, integrating or combining auditory and visual information is crucial for constructing unified percepts of the environment, and greatly enhances fundamental functions (e.g., object localization) as well as processes important for social communication (e.g., audiovisual speech recognition, Foxe et al., 2013). Using objective and sensitive measures of MSI, Chapter 2 revealed that participants with ASD have diminished and less efficient neural integration of basic audiovisual stimuli beginning as early as 100 ms post-stimulus over fronto-central scalp. At about 150 ms, audiovisual integration was completely absent in the ASD groups whereas it was widespread in the TD groups. Furthermore, behavioral indices of multisensory integration revealed that the children
with autism were less efficient at integrating information as reflected by decreased multisensory facilitation of reaction time compared to peers.

**The current investigation**

Here we ask whether the neurophysiological and behavioral measures of unisensory processing and multisensory integration derived in Chapter 2 can predict autistic symptom severity and visual/auditory sensitivities in a well-characterized sample of children and adolescents with ASD. Two separate multiple regression analyses are conducted for each of the two clinical outcome measures: 1) calibrated severity scores from the ADOS, and 2) the visual/auditory sensitivities scale of the Short Sensory Profile. One multiple regression examines the extent to which specific auditory ERPs (the P1, N1a, N1b, and N1c), visual ERPs (the P1 and N1), and three electrophysiological responses associated with audiovisual integration (between 100-210 ms) account for the variability seen in the two clinical outcome measures. The second regression assesses whether specific behavioral measures (reaction times to the auditory, visual, and audiovisual stimuli, as well as a psychophysical index of audiovisual integration) are helpful in predicting either of the two clinical outcome measures. Because certain demographic variables have been shown, albeit inconsistently, to correlate with the expression and severity of ASD (Gotham et al., 2009; Howlin, Goode, Hutton, & Rutter, 2004; Sell, Giarelli, Blum, Hanlon, & Levy, 2012; van Eeghen et al., 2013) and of sensory sensitivities (Ben-Sasson et al., 2009; Engel-Yeger, Hardal-Nasser, & Gal, 2011; Gouze, Hopkins, LeBailly, & Lavigne, 2009), participant characteristics (age, verbal IQ, performance IQ, sex, maternal education, and race) are considered in these analyses. Participant characteristics that show a direct relationship with ASD symptom severity or visual/auditory sensitivities are controlled for in the analysis by entering them as first stage variables in a hierarchical regression.
Materials and Methods

Participants

Data from 52 individuals with ASD between the ages of 6-16 years were analyzed. Nine of these participants were excluded from the analysis of autism symptom severity because they were administered an ADOS Module 4 (which is for adolescents and adults with fluent speech), and at this time CSS are not available for Module 4. Thus, data from 43 individuals were included the analysis of CSS. Six individuals were excluded from the analysis of visual/auditory sensitivities due to missing data from the Short Sensory Profile, resulting in a total N=46 for this analysis.ADOSes were administered and scored by a research-reliable psychologist or trainee, and an ASD diagnosis was confirmed with a developmental history and clinical judgment.

Intellectual functioning was assessed using the Wechsler Abbreviated Scales of Intelligence (WASI, Wechsler, 1999). Table 2 describes the intellectual makeup of the full sample. Ethnicities represented in the full dataset included 15% African American, 8% Asian American or Pacific Islander, 67% Caucasian, 2% Native American, 4% multiple races, and 4% did not report race. 21% of mothers reportedly had an education at or below the high school level, 42% of the sample reported maternal education at the college level, and 37% reported a maternal education at the graduate or professional level. Exclusionary criteria included a history of seizures (non-febrile) or head trauma, a performance IQ estimate below 80, or a known genetic disorder. Participants had normal hearing and normal or corrected-to-normal vision.

Informed written consent was obtained from each participant's parent or legal guardian prior to entering into the study. Verbal or written assent was obtained from each participant. All procedures were approved by the Institutional Review Boards of the Albert Einstein College of
Medicine, the City College and the Graduate Center of the City University of New York, and were in accord with the ethical standards laid out in the declaration of Helsinki.

<table>
<thead>
<tr>
<th>Age</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>6-17 years</td>
<td>55-150</td>
</tr>
<tr>
<td>Mean (S.D.)</td>
<td>11.2 (2.9)</td>
<td>100 (21)</td>
</tr>
</tbody>
</table>

Table 2. Range, mean, and standard deviations of age, verbal and performance IQ for the 52 participants included in this analysis. 'Verbal IQ' and 'Performance IQ' as assessed by the Wechsler Abbreviated Scale of Intelligence (WASI).

**Procedure**

Clinical assessments, including the ADOS, WASI, and Sensory Profile, were administered at the participant's initial visit to the laboratory. On the following visit, participants performed a simple reaction time task while continuous electroencephalography (EEG) was recorded. The parameters of the task and the ERP acquisition, processing and analysis procedures were identical to those detailed in Chapter 2. They are briefly described here.

**Audiovisual simple reaction time task.** While seated at a computer in a dimly lit, sound attenuated room, participants performed a simple reaction time task that consisted of three stimulus conditions presented with equal probability: 'auditory-alone' (a 1000-Hz tone of a 60 ms duration and 75 dB SP), 'visual-alone' (a red disc with a diameter of 3.2 cm appearing the black background of a computer monitor), and 'audiovisual' (simultaneous presentation of the 'auditory-alone' and 'visual-alone' stimuli). Auditory stimuli were presented from a speaker located centrally atop the computer monitor, and the visual stimuli were presented from a computer monitor centered 122 cm in front of the participant. The three stimulus conditions
were presented in random order with an inter stimulus interval (ISI) that varied randomly between 1000-3000 ms to decrease predictability of the timing of the stimulus presentation. Participants were instructed to press a button on a response pad as quickly as possible when they saw the circle, heard the tone, or saw the circle and heard the tone together. The same response key was used for all the three stimulus types. Stimuli were presented in blocks of 100 trials each, and participants completed between 9 and 11 blocks (with the vast majority completing 10 blocks).

**ERP Acquisition.** Continuous electroencephalography (EEG) was recorded from 70 scalp electrodes at a digitization rate of 512 Hz using the BioSemi ActiveTwo™ electrode system with an open pass-band from DC to 150 Hz. The continuous EEG was recorded referenced to a common mode sense (CMS) active electrode and a driven right leg (DRL) passive electrode. CMS and DRL, which replace the ground electrodes used in conventional systems, form a feedback loop, thus rendering them references (for a description of the BioSemi active electrode system referencing and grounding conventions, visit www.biosemi.com/faq/cms&drl.htm).

**ERP Processing and Analyses.** Matlab was used for offline processing and analyses. A low-pass filter of 45 Hz with a slope of 24 db/octave, and a high-pass filter of 1.6 Hz with a slope of 12 db/octave were applied to each participant’s continuous EEG. To generate ERPs, the EEG was divided into 600 ms epochs (100 ms pre-stimulus to 500 ms post-stimulus onset) with baseline defined as −50 to +10 ms relative to stimulus onset. Only trials for which the participant made a response (button press) within a specific time window were included in the analysis. Electrode channels with amplitudes larger than ±120 μV during the epoch surrounding stimulus presentation were considered to have excessive electromuscular activity, including
those resulting from large eye movements, and were interpolated on a trial-by-trial basis using the nearest-neighbor spline (Perrin et al., 1989; Perrin et al., 1987). Channels with a standard deviation of <0.5 μV across the block were interpolated on a block-by-block basis. Finally, if there were more than four bad channels in a trial, then the trial was rejected (i.e., no more than four channels were interpolated for any given trial). Epochs were sorted according to stimulus condition and averaged for each participant. The resulting auditory, visual, and audiovisual ERPs were re-referenced to an average of all electrodes. For each participant, a “sum” condition was created by summing together the auditory and the visual ERPs (from the unisensory conditions).

Clinical Measures.

1. Assessment of autism symptom severity. Calibrated severity scores (CSS) were derived from ADOS raw total scores using the conversion table in Gotham and colleagues (2009, p. 699). CSS are on a 1-10 point scale with higher numbers representing increased severity of autistic symptoms. A CSS under 4 is associated with a non-spectrum classification (Gotham et al., 2009). In this data set CSS ranged from 5-10. The distribution of scores within the sample is presented in Table 3.

2. Assessment of visual and auditory sensitivities. Visual/auditory sensitivity (VAS) scores were computed by mapping participants' classification on the VAS scale of the Short Sensory Profile onto an ordinal 0-2 point scale such that 0= 'typical development', 1= 'probable difference', and 2= 'definite difference'. The distribution of VAS scores within the sample is presented in Table 3.
Table 3. Distribution of Calibrated Severity Scores (CSS) and Visual and Auditory Sensitivities (VAS) within the sample. CSS are derived from the ADOS (Lord et al., 1999) and are on a 1-10 point scale with higher numbers representing increased severity of autistic symptoms. The VAS score is derived from the Shirt Sensory Profile (McIntosh et al., 1999).

**Predictor Variables**

**Neural indices of unisensory processing and multisensory integration.** The peak amplitudes of the auditory P1, N1a, N1b, and N1c were used as measurements of early auditory processing, and the peak amplitudes of the visual P1 and N1 were used as measurements of early visual processing. The latencies and electrodes used to identify the peak amplitudes of these signature components were chosen *a priori* based on where these components were readily observable in Chapter 2. Electrophysiological indices of multisensory integration were based on the difference between the peak amplitudes of the audiovisual and sum conditions (a commonly used measure of multisensory processing; e.g., Brandwein et al., 2011; Foxe et al., 2000; Giard & Peronnet, 1999; Molholm et al., 2002; Murray, M. M., Molholm, et al., 2005; Russo et al., 2010; Teder-Salejarvi, W. A. et al., 2002). The three multisensory peaks included in this
analysis were also based on findings from Chapter 2 which showed MSI between 100-120 ms over fronto-central scalp, 100-130 over parietal scalp, and 180-210 over parieto-occipital scalp in the ASD participants.

**Psychophysical indices of unisensory and multisensory processing.** Participants’ mean reaction times (RTs) to each stimulus condition (auditory, visual, and audiovisual) were used as behavioral measures of speed of unisensory and multisensory processing. When calculating mean RTs, outlying trials, defined as RTs falling over 2 standard deviations from an individual’s mean RT, were excluded. Maximum race model violation was used as the behavioral metric of audiovisual integration (Miller, J., 1982). An in-depth explanation of the race model and its application to studying multisensory integration is presented in Chapters 1 and 2. In brief, the race model assumes that the facilitation of response times to multisensory stimuli (compared to unisensory stimuli) occurs because multisensory stimuli have two inputs (e.g., auditory and visual) and the fastest input wins (a process referred to as probability summation). However, if RTs to multisensory stimuli are significantly faster than predicted by probability summation, the race model is considered to be violated and RT facilitation is assumed to be due to the interaction of unisensory inputs during processing. Here, maximum race model violation is defined as the largest ’Miller inequality’ value (as calculated in Chapter 2) across the first third of the distribution of RTs for each individual.

**Participant Characteristics.**

Age, sex, race, maternal education, and estimated verbal IQ (VIQ) and performance IQ (PIQ) of participants were considered in the analyses. Race was coded as a categorical variable with 6 levels (African American, Asian American or Pacific Islander, Caucasian, Native American, multiple races, and no reported) and maternal education as an ordinal variable with 3
levels (at/below the high school level, college level, and graduate/professional level). Estimates of VIQ and PIQ were measured by the WASI.

**Statistical Analysis**

**Consideration of participant characteristics.** An initial correlation analysis was performed to assess whether there were any significant relationships between the demographic characteristics of participants and the two clinical outcome measures. Participant characteristics that were shown to correlate with CSS or VAS were controlled for in the regression analyses by entering them into a hierarchical regression as 'stage 1' variables. The preliminary correlation analysis on this dataset showed that none of the participant characteristics considered were significantly related to CSS. VIQ was shown to be significantly related to VAS ($r (46) = -.414, p<.01$) such that a lower VIQ was associated with higher levels of visual and auditory sensitivities. In order to control for the potential effect of VIQ on predicting VAS scores, VIQ was entered in Step 1 of the hierarchical regressions.

**Predicting autism severity.** Two linear regression analyses were conducted to assess the extent to which 1) neurophysiological measures, and 2) behavioral measures, can predict autism symptom severity as measured by CSS. In the first regression, the nine ERP measures of auditory and visual processing and integration were entered into a simple linear regression as independent variables with CSS as the dependent variable. In the second regression analysis, the four behavioral measures were entered into a simple linear regression as independent variables with CSS as the dependent variable. The change in $R^2$ associated with the linear combination of the independent variables was used to evaluate the extent to which neurophysiological and behavioral measures of sensory processing and integration predict autistic symptom severity.
The importance of individual ERP components and of behavioral response patterns was considered by examining their relative contribution to the variance in CSS.

**Predicting visual and auditory sensitivities.** Two hierarchical regression analyses were performed to assess the extent to which 1) neurophysiological measures, and 2) behavioral measures, can predict visual/auditory sensitivities (as measured by VAS scores), above and beyond that predicted by VIQ. For both of the regression analyses VIQ was entered in Step 1 of the regression analysis, as a preliminary analysis suggested that increased visual/auditory sensitivities are correlated with a lower IQ. The nine ERP measures were entered in Step 2 for the regression examining neurophysiological predictors. Similarly, the four behavioral measures were entered in Step 2 for the regression assessing behavioral variables. The change in $R^2$ resulting from the addition of the ERP and behavioral variables was used to evaluate the extent to which these experimental indices predict visual and auditory sensitivities once VIQ is controlled for. The importance of individual ERP components and of behavioral response patterns was considered by examining their relative contribution to the variance in VAS.

**Results**

**Analysis 1: Predicting Autism Symptom Severity**

**Neurophysiological Predictors.** The linear combination of the nine ERP measures was significantly related to CSS, $F (9, 33) =2.925, p=.012$. The $R^2$ of .444, indicated that approximately 44% of the variance of autistic symptom severity in the sample can be accounted for by the linear combination of ERP measures (as depicted by the regression scatter plot in Figure 1). Table 4 presents the relative strength of the individual predictors. The auditory N1a and the auditory N1b were the strongest unisensory ERP predictors of CSS. The negative correlation between the N1a and CSS suggested that a smaller N1a (e.g., a more positive
amplitude value) was associated with less severe symptoms (lower CSS). The positive correlation between the N1b and CSS indicated that a larger N1b (e.g., more negative amplitude value) was associated with less severe symptoms (lower CSS). MSI between 100-130 ms over parietal scalp significantly contributed to the variance observed in CSS. Larger MSI effects were associated with less severe symptoms.

Figure 1. Scatterplot displaying the relationship between the symptom severity, as measured by the Calibrated Severity Scores (CSS) of the ADOS (y-axis) and the linear combination of nine ERP peaks measuring auditory, visual, and audiovisual processing (x-axis). Each point represents a single value for a participant. The p value associated with the $R^2$ of .444 is .012.
The Bivariate and Partial Correlations of the ERP predictors with CSS

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Correlation between each predictor and CSS</th>
<th>Correlation between each predictor and CSS controlling for all other predictors</th>
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</thead>
<tbody>
<tr>
<td>Auditory P1</td>
<td>.219</td>
<td>-.155</td>
</tr>
<tr>
<td>Auditory N1a</td>
<td>-.333*</td>
<td>-.345*</td>
</tr>
<tr>
<td>Auditory N1b</td>
<td>.436**</td>
<td>.472**</td>
</tr>
<tr>
<td>Auditory N1c</td>
<td>-.069</td>
<td>-.076</td>
</tr>
<tr>
<td>Visual P1</td>
<td>.020</td>
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</tr>
<tr>
<td>Visual N1</td>
<td>-.175</td>
<td>-.025</td>
</tr>
<tr>
<td>MSI Peak 1</td>
<td>-.044</td>
<td>-.129</td>
</tr>
<tr>
<td>MSI Peak 2</td>
<td>-.342*</td>
<td>-.419*</td>
</tr>
<tr>
<td>MSI Peak 3</td>
<td>.152</td>
<td>.073</td>
</tr>
</tbody>
</table>

Table 4. *p < .05    **$p = .005$

For descriptive purposes only, waveforms were generated in order to visualize the auditory N1a, N1b, and the parietally focused MSI peak (between 100-130 ms), which were the three ERP effects that were significantly related to CSS. Participants were separated into two groups: moderate and severe symptoms of ASD. Participants with a CSS between 5-7 (N=22) were in the ‘ASD-moderate’ group and those with a CSS between 8-10 (N=22) were in the ‘ASD-severe’ group. The two groups did not differ significantly in age, or estimates of PIQ and VIQ. ERPs from a comparison group of age and PIQ matched typically developing children were also plotted to visualize how the waveforms of the ‘ASD-moderate’ and the ‘ASD-severe’
groups compared to those of TD children. Figure 2a shows that the peak of the auditory N1a in the ‘ASD-moderate’ group is midway between the peak of the auditory N1a in the ‘ASD-severe’ and the TD group. The auditory N1b component (Figure 2b) in the ‘ASD-moderate’ group is very similar to, and in fact overlapping with that of the TD group. The auditory N1b is strikingly smaller in the ‘ASD-severe’ group. The parietally focused MSI peak between 100-130 ms is largest in the TD group and smallest in the ‘ASD-severe’ group, with the peak amplitude of the ‘ASD-moderate’ group falling midway between the severely autistic and the TD children (Figure 2c).

**Behavioral Predictors.** The linear combination of the four behavioral measures did not predict CSS, $F(4, 37) = .343, \ p = .847$.

**Analysis 2: Predicting Sensory Sensitivities**

**Neurophysiological Predictors.** The linear combination of the nine ERP measures did not account for a significant proportion of the variance in VAS scores after controlling for the effects of VIQ ($R^2$ change=.125, $F(9,35)=.691, \ p = .712$)

**Behavioral Predictors.** The linear combination of the 4 behavioral measures did not predict VAS scores after controlling for the effects of VIQ ($R^2$ change=.017, $F(4, 30) = .168, \ p = .953$).
Figure 2. Mean ERPs for the ASD-severe, ASD-moderate, and typically developing groups. Panels (a) and (b) depict the three groups’ responses to the auditory-alone condition, with dashed lines indicating the component of interest (the auditory N1a and N1b). Panel (c) depicts a measure of audiovisual integration, represented by a difference wave (explained in the text). Dashed lines indicate the audiovisual peak of interest. Traces represent the composite signal from two adjacent electrodes, the locations of which are indicated on the head models.

Discussion

This study investigated the presence of a relationship between neurophysiological metrics of early sensory processes and clinically significant symptoms associated with autism. The data
revealed that a combination of neural indices of auditory and visual processing and integration were predictive of severity of autistic symptoms in a group of children and adolescents with ASD. A particularly robust relationship was observed between severity of autism and the integrity of basic auditory processing and audiovisual integration. That is, more typical neural responses were associated with lower severity scores. In contrast, our physiological indices did not predict visual/auditory sensitivities as assessed by parent responses on a questionnaire.

**Autism Symptom Severity**

The strongest neurophysiological predictors of autistic symptom severity were the auditory N1a and N1b. These components of the auditory N1 complex reflect basic auditory processing and typically show extensive developmental changes over childhood (Ceponiene et al., 2002; Gomes et al., 2001; Ponton et al., 2000; Tonnquist-Uhlen, Ponton, Eggermont, Kwong, & Don, 2003). In young children (generally under nine years of age), the N1 is most prominent at lateral electrode sites. The fronto-centrally focused N1b, which is the most prominent negative peak in adults, matures during middle childhood. The findings from our developmental study (Chapter 1) are consistent with this developmental trajectory in showing that the amplitude of the lateral negative components decreased with age, and that the amplitude of the fronto-central component increased with age. In light of these documented changes in N1 morphology, our current observation that increased severity of autism is associated with a larger lateral N1 and a smaller fronto-central N1 is suggestive of immature responses to auditory stimuli during the early stages cortical processing.

The notion that auditory processing deficits are an important component of ASD is not new, but the nature of such deficits remains unclear. Several neurophysiological studies have shown atypical auditory processing of tones in ASD (Bruneau, Roux, Adrien, & Barthelemy,
1999; Dunn, M. et al., 2008; Oades, Walker, Geffen, & Stern, 1988); however, results have been conflicting and confusing. For example, Bruneau and colleagues (1999) found smaller N1b amplitude in children with ASD while Oades and colleagues (1988) found that the N1b was larger and had a shorter latency. To further complicate the picture, a number of studies failed to find differences in obligatory sensory ERPs to non-social sounds in ASD groups, compared to controls (Dunn, M. et al., 2008; Gomot, Giard, Adrien, Barthelemy, & Bruneau, 2002; Lincoln, Courchesne, Harms, & Allen, 1995; Novick, Vaughan, Kurtzberg, & Simson, 1980; Salmond, Vargha-Khadem, Gadian, de Haan, & Baldeweg, 2007). Inconsistent findings in the literature are likely related in part to participant characteristics (age, cognitive level, etc.) and experimental parameters (e.g., inter-stimulus interval, and active versus passive tasks; see Dunn, M. et al., 2008), which vary greatly between studies. The current study was not designed to disentangle these variables or to provide additional data on how TD and ASD children differ, but rather to assess the relationship between the core symptoms of autism and electrophysiological indices of sensory processing. Examining these processes in a group of individuals whose symptom severity level ranged from moderate to severe revealed that there is variability in basic measures of auditory processing within individuals on the autism spectrum. This is true even in a sample with a relatively wide range of intellectual abilities. Our results suggest that the variability in auditory evoked potentials is related to differences in severity of autism. With this in mind, we suspect that taking into account symptom severity might help in understanding some of the inconsistencies in the literature regarding basic auditory processing in ASD.

**Why focus on auditory processing?** Of all the sensory systems, audition is the most frequently studied in ASD, perhaps because of its obvious association with spoken language. It has been hypothesized that aberrant processing of sounds contributes to atypical language and
communication development in autism (for a review see Bomba & Pang, 2004; DePape, Hall, Tillmann, & Trainor, 2012; Russo, Nicol, Trommer, Zecker, & Kraus, 2009; Whitehouse & Bishop, 2008). It is not possible to know from the current dataset whether or not the auditory ERP effects are related to language ability (since language level was not directly analyzed); however, it is likely that language is in some way entangled in this relationship. The extent to which language level directly contributes to our independent measure (CSS) is minimized through the modular structure of the ADOS (which takes into account the individual's language level); but the CSS are not completely independent of language level (Shumway et al., 2012). Thus, we cannot eliminate the possibility that the association between our neural markers of auditory processing and symptom severity is mediated by some aspect of language. In fact, emerging data support a relationship between neurophysiological markers of basic auditory processing and language impairment in ASD (Oram Cardy, Flagg, Roberts, & Roberts, 2008; Roberts et al., 2010).

**Multisensory Integration.** Here we showed that a measure of audiovisual integration over parietal scalp (in the 100-130 ms post-stimulus time window) accounted for some percentage of the variability in severity of clinical presentation. Though little is known about the functional role of this MSI effect, our finding that it is smaller in individuals with more severe autism supports the thesis that deficits in MSI are associated with the core symptoms of autism. This MSI effect is independent of the abnormal auditory processing discussed above because our analyses controls for individual differences in unisensory processing. Our finding that reduced MSI predicts more severe symptoms of ASD can be understood in a number of ways. From a developmental perspective, suboptimal communication between sensory cortices, if present at an early age, could have cascading effects on the development of language and social skills. For
example, early language learning involves combining incoming visual (lip movements) and auditory (speech sounds) information, a process that is typically accomplished seamlessly. It is not hard to imagine how difficulties integrating auditory and visual cues might delay or interfere with the typical development of language which is a common characteristic of individuals on the autism spectrum (e.g., Foxe et al., 2013).

A large part of pragmatic or social language is based in multimodal communication; for example, gestures are combined with words, and facial expressions with prosodic vocal changes. Deficits in perceiving and producing these more nuanced forms of communication are hallmark symptoms of ASD. Because these symptoms are part of an entrenched social impairment that extends well beyond the language domain, they probably cannot be explained solely by deficits in multisensory integration. However, it may be that individuals with a pervasive social impairment who lack adequate social engagement may need to rely more on their sensory experiences and on redundant sensory inputs to learn social cues than do typically developing individuals. Those with a reduced ability to properly combine and perceive multisensory inputs may be at a greater disadvantage, as they may not learn that certain stimuli (e.g., facial expressions, vocal intonation) go together. It is in this way that deficits in MSI may exacerbate the severity of symptoms seen in ASD.

Another possibility is that some individuals who have trouble integrating stimuli from multiple modalities are overwhelmed by the amount of incoming information, and react by withdrawing from their environment. With a decreased ability to make sense of the sensory inputs, individuals may develop strange self-regulatory behaviors as a means to cope with so-called ‘sensory overload’. Deficits in sensory integration may contribute to the increased withdrawal and the unusual sensory behaviors that are often seen in more severe autism. Of
course, these explanations are all highly speculative and are difficult hypotheses to address empirically.

**Clinical Questions.** From a research perspective, our experimental findings provide compelling evidence that the core deficits of autism are related to very basic neurophysiological processes involved in sensory registration and integration. Clinically, a question that naturally arises is, how do these findings relate to the autism phenotype? That is, what do these children with larger auditory N1a components or smaller auditory N1b components ‘look like’? How do they present to clinicians? The short answer of course is that they present with more severe autism, but what exactly does that mean? Here, the construct of autism severity is represented by a single score derived from clinicians’ observations of the child’s social affect and restrictive and repetitive behaviors. The 10 items that comprise the social affect domain include ratings of the child’s communication and reciprocal social interactions. For example, children are judged on their use of gestures and facial expressions, the quality of their eye contact, and their initiation of joint attention. Overall quality of rapport, social overtures and social responses also contribute to scores. Restricted and repetitive behaviors include symptoms such as stereotyped/idiosyncratic use of words and phrases, unusual sensory interests, hand and finger and other complex mannerisms, and unusually repetitive interests or stereotyped behaviors. While the severity scores are designed so that a higher severity score indicates that the individual has a greater number of the core symptoms described above, and/or a more severe impairment of these core symptoms (Gotham et al., 2009), the scores do not inform us of the individual’s specific areas of impairment. An important next step will be to separate out the two symptom domains that contribute to the severity score and investigate whether our neurophysiological measures are better predictors of impaired social affect or of restricted and repetitive behaviors.
Visual/Auditory Sensitivities

Whereas our neurophysiological indicators of sensory processing and integration were good predictors of autism severity, they showed no systematic relationship with auditory and visual sensitivities as rated by parents. It is tempting to interpret this finding as lack of evidence for a neurophysiological basis for auditory and visual sensitivities in ASD. However, such an interpretation is premature for a number of reasons, the most significant of which being the measurement we used to quantify visual/auditory sensitivities. The Short Sensory Profile (SSP) was chosen as an outcome measure because it is currently the most commonly used scale of sensory processing in research; nevertheless, it is far from ideal. Like most parent report measures, the SSP is problematic because parents can be strongly influenced by the symptoms they believe to be related to their child's disorder (Dahlgren & Gillberg, 1989), as well as by their own personal experiences with sensory stimuli. In addition, the psychometric properties of the SSP are poor (small sample size across a large age range) and there are no age or IQ-specific normative data, which is particularly important to have given the known influences of age and cognitive level on sensory responses and behaviors (Crane et al., 2009; Kern et al., 2006). While the shortcomings of the SSP limit the conclusions that can be made from the current dataset, these issues highlight the need for an improved measure of sensory symptoms. Establishing a valid measure of sensory symptoms is important not only for research purposes, but also for use by clinicians. This is especially the case in light of the inclusion of sensory symptoms in the DSM-5.

Future Directions

As touched upon in the introduction, a strength of this study is its implications for identifying biomarkers of ASD. Clinical diagnosis is currently made on the basis of behavioral
characteristics and symptoms which can be highly subjective and often require a tremendous amount of clinical expertise. On the other hand, biomarkers (whether they are genetic, neuroanatomical, or in this case neurophysiological) are measured objectively and systematically. Biomarkers may prove invaluable in sub-grouping this incredibly heterogeneous disorder, aiding in early identification of at-risk individuals, and developing targeted, individualized interventions. While there is much ground to be covered in terms of identifying candidate endophenotypic markers of ASD, the hope is that combining our robust neurophysiological indices of basic sensory processing with well-established clinical measures of autism, will help get us closer to this point. Findings from the current study suggest that further investigation of cortical auditory ERPs (the N1 in particular) have the potential to contribute significantly to the development of biomarkers and to increase our knowledge of brain function, genetics, sensory processing, and development in general.
GENERAL DISCUSSION

Overview and Summary

This series of studies investigated the cortical dynamics of audiovisual integration across typical development, and in high-functioning children with autism spectrum disorder (ASD). A commonly held belief is that many individuals with ASD process sensory information differently from others, with atypical processing and integration of sensory inputs interfering with perceptual experiences, and resulting in unusual sensory responses and interests. The studies reported in this thesis are among the first to directly investigate the neural processes underlying these suspected impairments in multisensory integration (MSI), and to focus directly on the integration of very basic, non-social stimuli. By using high-density electrophysiological and reaction time measures, we were able to assess whether or not, and to what degree, individuals with ASD have deficits in sensory processing and integration at the earliest stages of cortical processing. By undertaking these studies, we provide a window into the relationship between basic neural processes, and the complex social and cognitive deficits and unusual sensory behaviors characteristic of ASD.

Chapter 1

The first study in this volume characterized the developmental trajectory of audiovisual integration in typically developing individuals ranging in age from 7 years old through adulthood. By including children and adolescents, this study fills an important gap in multisensory research, which has largely focused on adults and animals. Among our findings were that behavior revealed a gradual fine-tuning of multisensory facilitation of performance on a reaction time task across middle childhood. Although participants in all age groups benefited
from the simultaneous presentation of auditory and visual cues, adult-like multisensory facilitation of behavior was not reached until adolescence (13-15 years). A similarly protracted period of maturation was seen in the brain processes underlying MSI.

The systematic relationship between our neurophysiological and behavioral data strongly suggests that observed improvements in multisensory facilitation over middle childhood are rooted in maturational changes in the brain. These changes may reflect prolonged plasticity of those neural networks sensitive to the young child's exposure to multisensory experiences. Though this experiment was not designed to assess the role of experience in the neural development of MSI, our data support the "developmental integration" view which posits that the functional connections between sensory systems develop gradually as the direct result of the child's interactions with multisensory experience (as described by Lewkowicz, D. J. & King, 2012). One can also think about the emergence of more adult-like integration as reflecting the general neural reorganization (e.g., overall changes in cortical gray and white matter density) that occurs during late childhood and adolescence (Giedd et al., 1999; Sowell, Thompson, Tessner, & Toga, 2001). In examining typical development, this study sets the stage for our investigation of MSI in ASD.

Chapter 2

The second study in this thesis examined MSI in children and adolescents with ASD. A key question was whether children and adolescents with ASD exhibit deficits in audiovisual integration at early, sensory level stages of cortical processing. Unlike earlier research we focused on non-social stimuli to better understand whether these suspected deficits are independent of more general difficulties processing social information. The picture that emerged
from our behavioral and electrophysiological data is that, relative to their healthy peers, individuals with ASD rely on different and less effective neural networks to integrate auditory and visual inputs. Considering the early timing of the observed MSI deficits, and the non-social nature of the stimuli, our observation of reduced neural integration suggests that information processing differences in ASD are not limited to social and higher-order cognitive processing, but rather that they are already in action during early stages of sensory processing and integration.

In keeping with the contemporary view that early MSI arises in part through neural connections between long distance connections between sensory areas, our finding of reduced MSI in ASD (Chapter 2) fits well with the theory that the neural circuitry involved in integrating information from distant brain regions is disordered in ASD. Connectivity models (of which there are several variants) suggest that autism is associated with abnormal neural connectivity characterized specifically by reduced long-distance connections (i.e., between spatially distant brain regions) and increased local connectivity (particularly within the frontal cortex) (Belmonte et al., 2004; Courchesne & Pierce, 2005b; Just et al., 2007; Just et al., 2004; Muller et al., 2011; Uddin, Supekar, & Menon, 2013; Wass, 2011). Perceptual and cognitive functions that rely on the integration and coordination of information are thought to be impaired in ASD due to decreased communication and under-connectivity between distant brain regions. A handful of studies indicate that more severely affected individuals with ASD show reduced long-distance connectivity (Assaf et al., 2010; Just et al., 2007; Kleinhans et al., 2008; Monk et al., 2009; Poustka, Jennen-Steinmetz, Henze, Stieltjes, & Cimh, 2011; Weng et al., 2010). Our finding that symptom severity is associated with the cortical circuitry involved in integrating inputs from the
spatially distant auditory and visual cortices (Chapter 3) lends additional support to the hypothesis that disordered neural connectivity underlies the core symptoms of ASD.

While Chapter 2 did not directly analyze cortical connectivity, the results do suggest that suboptimal coordination and interaction between specialized brain regions occurs at a relatively early stage of sensory processing. An important next step is to utilize methods that can directly assess whether or not these early deficits in basic audiovisual integration are associated with reduced functional connectivity between sensory cortices. We suspect that the connections between auditory and visual brain regions are weaker in individuals with ASD and that these abnormalities are related to suboptimal performance on tasks that pull for fast and efficient integration of inputs. If we find this to be the case, it will be of great interest to explore the extent to which these specific low-level sensory integration deficits are part of a more general and widespread pattern of reduced cortical connectivity in ASD. That is, are we dealing with a specific deficit in the cortico-cortico connections that underlie audiovisual integration, or is this one sign of an overall 'disconnected' brain?

*Methodological Consideration:* One explanation for our finding of reduced audiovisual integration in ASD (Chapter 2) is that the stimuli in this experiment were not optimized to elicit MSI. According to the principle of inverse effectiveness, individuals benefit the most from multisensory inputs when the constituent unisensory inputs are weak. For example, Senkowski and colleagues showed, using a simple reaction task similar to that employed here, that in healthy adults, multisensory facilitation of reaction time and multisensory interactions (as measured by event related potentials or ERP) were greatest for low intensity auditory and visual stimuli (2011). It is possible that the intensity of the stimuli presented in our study (Chapter 2) was not sufficiently low enough to elicit clear multisensory interactions in ASD. Assuming this
is the case, we might speculate as to why the ASD group had a higher threshold for MSI than the typically developing group: it is possible that weak connections between auditory and visual regions lead individuals with ASD to rely more heavily on unisensory networks. If this is the case we might expect that it is only when the unisensory inputs are not strong enough to evoke a robust unisensory response that the weak inter-cortical connections are made use of. Studies that vary stimulus intensity (e.g., by changing the sound pressure level of auditory stimuli and the luminance of visual stimuli) are necessary to clarify these issues.

Chapter 3

It is a longstanding practice in research to compare clinical groups to control groups (e.g., a between groups design). As the heterogeneity of the ASD phenotype becomes increasingly apparent, the limitations of this approach are more and more evident in ASD research. In using one data point (a group mean) to represent a group with such a varied clinical presentation, we may not be capturing important within group differences. Chapter 3 was designed to go beyond the between groups analysis employed in Chapter 2, and explore whether the neurophysiological and behavioral differences we observed between the ASD and TD groups reflect behavioral symptoms associated with autism. We chose to characterize our group using severity scores from the Autism Diagnostic Observational Schedule (ADOS; Lord et al., 1999) because they represent the core symptoms of autism (qualitative deficits in social communication and restricted and repetitive behaviors); are relatively independent of cognitive ability, language level and age, and are based on clinical observations during a standardized administration rather than on parent report. Since we had a particular interest in understanding the relationship between our physiological measures of audiovisual processing and the unusual sensory behaviors frequently
associated with ASD, we also characterized our sample in terms of their Visual/Auditory Sensitivities as assessed by parent ratings on the Short Sensory Profile.

The data presented in Chapter 3 showed that electrophysiological measures of basic auditory and visual processing and integration were related to core autism symptomology. ERP components associated with low-level auditory processing and audiovisual integration stood out as particularly strong predictors of autistic symptom severity in our sample. Based on what is known about the typical developmental trajectory of early auditory components, the pattern of results here suggests that increased symptom severity in autism is associated with less mature neural responses to basic, non-social auditory stimuli at early stages of sensory processing. The nature of relationship between auditory processing and ASD symptoms is likely a complex one that cannot be answered by the current study alone. Our data indicate that a more thorough examination early auditory processing is warranted, and a good place to focus future investigations. Furthermore, it highlights the importance of taking into account symptom severity when assessing for auditory processing and audiovisual abnormalities.

Methodological Consideration: An important possibility to consider is that the observed relationship between autism severity and our neural measures of auditory and audiovisual processing is mediated by language. Language impairments have been associated with abnormal processing of auditory stimuli, both at the behavioral and neurophysiological level (e.g., Basu, Krishnan, & Weber-Fox, 2010; Bishop & McArthur, 2004, 2005; Lincoln et al., 1995; McArthur & Bishop, 2005; Ors et al., 2002; Webster & Shevell, 2004), as well as with severity of ASD (Constantino, Hudziak, & Todd, 2003; Gotham, Risi, Pickles, & Lord, 2007; Hus, Bishop, Gotham, Huerta, & Lord, 2013). An advantage of the ADOS is that it takes into account, and is relatively independent of an individual's verbal fluency and basic expressive language level. An
interesting question to ask is, to what extent are the severity scores in our sample related to language comprehension and more nuanced aspects of language. That is, how much of the variability in autistic symptom severity is accounted for by some aspect(s) of language? If language function does account for a significant amount of the symptom severity in our sample, do our neurophysiological correlates of sensory processing and integration predict severity over and above language function? In order to answer this question, it will be necessary to include a comprehensive language measure (such as the Clinical Evaluation of Language Fundamentals, Semel, Wiig, & Secord, 2003) in our analysis. Parsing the relationship between neurophysiological markers of sensory processing, ASD symptoms, and language impairment will likely prove valuable in understanding the role of language deficits in ASD as well as the suspected neurobiological overlap between ASD and specific language impairment (e.g., De Fosse et al., 2004; Williams, D., Botting, & Boucher, 2008 for a discussion of this topic). If we can differentiate these disorders at a neurobiological level there is the potential to more appropriately intervene in the cases of a subgroup of very young children for whom making a differential diagnosis is more difficult.

**The larger picture**

We came into this project with the goal of characterizing the functional integrity of the cortical processes that underlie basic audiovisual integration in high-functioning children with ASD. We showed that these processes are atypical at a very fundamental neurophysiological level, and are associated with suboptimal performance. Furthermore our data reveal a relationship between basic sensory processes and the core symptoms of ASD. These results lead us to speculate that some of the perceptual and cognitive deficits observed in autism arise from aberrant activity at the early stages of sensory processing and integration. One possibility, as
considered above, is that weak neural connections between so-called sensory cortices interfere with the typically seamless integration of auditory and visual inputs. When the audiovisual information, whether it be very basic (e.g., shapes and tones) or socially complex (e.g., a real life interpersonal interaction), is not adequately combined early on in the processing stream there may be consequences for subsequent processing. At this point the nature of these consequences and how they unfold is not clear. We know that children with ASD reap some benefit from the presence of corresponding multisensory inputs, but not to the same degree as their typically developing peers (Brandwein et al., 2013; Foxe et al., 2013; Irwin et al., 2011; Smith & Bennetto, 2007). These performance differences may be the result of cascading effects of inefficient processing that began at the early stages of sensory integration.

**Future Directions**

**Mapping the continuum from low-level basic sensory integration to higher-order social processing.** Throughout this thesis we emphasized the importance of studying basic, sensory-level MSI because we suspect that higher-level integration of audiovisual information (such as AV speech perception) necessarily depends in part on the integrity of these early sensory processes. The findings presented in Chapter 2 suggested that the cortical networks involved in the early stages of multisensory processing are compromised in high-functioning children and adolescents with ASD. A crucial next step is to explore the extent to which these low-level audiovisual integration deficits are related to higher-level processes. A key question that arises is: does the ability to integrate simple stimuli early on in the processing stream form the basis for the capacity to combine complex, social stimuli at a cognitive and social level? Surely there is some relationship between the two: but is it measurable with the standard experimental paradigms, and do our electrophysiological indices of MSI capture it? What do our
findings, and those of others looking at basic MSI, tell us about an individual’s ability to process multisensory audiovisual social stimuli related to communication, and how does this differ in ASD?

One possibility is that the ability to integrate socially complex audiovisual stimuli, such as seen and heard speech, relies on the same neural networks as those involved the integration of non-social stimuli, such as circles and tones. Given our findings from Chapter 2, which showed reduced and inefficient neural integration of basic audiovisual stimuli in high-functioning children and adolescents with ASD, we might expect this group to have significant impairments on performance on tasks of audiovisual speech perception. However, a recent 'speech in noise' study from our research group, which was based on a sample that overlapped with the sample used in Chapter 2, painted a more complex picture. Using a cross-sectional approach Foxe and colleagues (2013) showed severe multisensory speech integration deficits in children with ASD. Remarkably, these behavioral deficits were absent in the adolescent group. What can we make of this apparent 'recovery' of audiovisual speech perception? If we assume that audiovisual speech perception relies on the same underlying circuitry as basic audiovisual integration (which was shown, in Chapter 2 to be deficient in adolescents with ASD), we could speculate that the fundamental neural connections that supported the integration of auditory and visual speech signals during the 'speech in noise' task were also reduced in the adolescents with ASD. In this scenario, the adolescents' seemingly typical performance on the AV speech integration task emerged from a fundamentally different set of neural processes and circuitry than their healthy peers (Foxe et al., 2013). This might suggest that as children with ASD mature into adolescence they develop ‘work around’ strategies. That is, they arrive at the same behavioral endpoint through a different neurophysiological or behavioral route. They may employ some
compensatory strategy – perhaps ‘higher order’ processes and prior experience with talking faces, that allow the adolescents with ASD to make up for their low-level integration deficits. This would be a remarkable finding with implications for intervention at the learning and behavioral level. But, we are making a number of assumptions here as we do not yet know the relationship between low-level integration (e.g., detection and registration of audiovisual stimuli) and higher-order integration (e.g., perception and integration of meaningful multisensory information).

Going forward we need to 1) examine the extent to which ERP and behavioral measures of basic audiovisual integration can inform us of higher-order, more naturalistic aspects audiovisual processing, and 2) at which level of the processing stream, and for what types of stimuli, individuals with ASD deviate from their healthy peers, and 3) relate experimental findings to the real-life behaviors thought to be associated with deficits in sensory processing and integration. To meet these goals we propose a repeated measure design that compares, at a single subject level, performance across several different, but related, paradigms. Behavioral and neurophysiological responses will be compared on a series of audiovisual simple reaction time (AVSRT) tasks and on the well-established 'speech in noise' paradigm (e.g., Foxe et al., 2013; Ross, L. A. et al., 2011; Ross, L. A., Saint-Amour, Leavitt, Javitt, et al., 2007). Together these experiments will systematically probe different levels of audiovisual integration by employing stimuli of increasing social complexity. Moving successively from unassociated, non-social stimuli (tones and circles) to intrinsically related stimuli (e.g., a honking car), to socially rich stimuli (audiovisual speech) will allow us to flesh out the role that stimulus type plays at very fundamental and early stages of multisensory integration. In order to assess whether experimental results relate to real-life behaviors, participants’ experimental data will also be
compared, at an individual subject level, to scores on standardized clinical instruments. It will be important to include a range of assessments that reflect both clinicians' observations (e.g., ADOS severity scores: both Social Affect and Restrictive and Repetitive Behaviors, Hus, Gotham, & Lord, 2012), as well as parent report questionnaires (such as the Social Responsiveness Scale, Constantino, 2012; The Repetitive Behavior Scale - Revised, Lam & M.G., 2007; and the Short Sensory Profile, McIntosh et al., 1999), and when appropriate, self-report measures (e.g., Adolescent/Adult Sensory Profile, Brown & Dunn, 2002). This will provide a valuable opportunity to explore what, if any, aspects of neurophysiological abnormalities in sensory processing predict specific aspects of behavioral functioning.

**An expanded developmental approach.** The vast majority of neurophysiological research presented in this dissertation was based on children, adolescents, and adults with ASD. Considering that ASD is a disorder that unfolds during the first few years of life, the importance of studying neural processes, which must precede behavioral deviations, in very young children with (and at risk for) ASD cannot be overstated. Studying neural development during the early years is especially important given that the brain systems involved in basic sensory processes are thought to mature more rapidly and earlier in development than those associated with more higher order brain functions (Courchesne et al., 2005). By limiting studies to older children we are missing precisely that critical period in which the fundamental neural architecture that we suspect is responsible for abnormal sensory processing and integration is laid down. To emphasize this point we refer to the mounting evidence that very young children with ASD show substantial deviations in brain development over the first few years of life (reviewed by Courchesne & Pierce, 2005a). For example, imaging research has shown that infants and toddlers with ASD symptoms exhibit a period of excessive and accelerated brain overgrowth
followed by an atypically reduced rate of brain growth. A pressing question is to what extent anatomical (macro- and micro-structural) deviations in brain development relate to the specific underlying neural processes that contribute to the autistic phenotype. ERP studies have the capacity to address this question, but we must be prepared to study young children--as young as possible. High-density electrical mapping techniques are suitable and generally well-tolerated by infants (Johnson et al., 2001), and their feasibility in infant research is evident from the numerous ERP studies of auditory processing in infants (e.g., Dehaene-Lambertz & Dehaene, 1994; Dehaene-Lambertz & Pena, 2001; Jing & Benasich, 2006; Lippe, Martinez-Montes, Arcand, & Lassonde, 2007; Mai et al., 2012). The more challenging aspect of conducting neurophysiological studies of young children is adapting paradigms--particularly those that require the participant to look at a stimulus (i.e., investigations of visual or audiovisual processes). In such instances, computerized eye-tracking is a valuable tool that can document trials in which the participant looks at the stimulus.

With some modifications it is possible to apply AVSRT to examine the integrity of basic audiovisual processing and integration in infants, toddlers and young children. Eye-tracking can be added to the AVSRT task to document trials in which the child spontaneously foveates on the red circle, or alternatively the presentation of the visual stimulus could be contingent on the child looking at the computer monitor. This modification is not without drawbacks, the most significant of which is the lack of a behavioral metric (e.g., reaction time) to assess multisensory facilitation of behavior. Still, elucidating the neural representation of sensory processing and integration during the first few years of life is crucial to tracking potential deviations in the development of these elemental brain processes. Considering that learning and brain plasticity extends into adulthood, it behooves us to broaden our age range to include adults. This need is
highlighted by the growing number of studies showing normal to near normal performance by adolescents and adults with ASD on a variety of behavioral tasks as well as on neural measures (Courchesne, Muller, & Saitoh, 1999; Creasey et al., 1986; Foxe et al., 2013; Keane, Rosenthal, Chun, & Shams, 2010; van der Smagt et al., 2007).

The most powerful approach to examining any developmental process is to follow the same individual at several points in development. Employing a longitudinal design is particularly important in autism research because of the substantial individual variability in the emergence and presentation of symptoms over the lifespan. While ASD is generally considered a lifelong disorder, improvements in symptom severity and changes in diagnosis over childhood have been documented for some children (e.g., Fein et al., 2013; Gotham, Pickles, & Lord, 2012). The extent to which these improvements are represented in the brain is not known. Using a longitudinal approach to investigate the neurobiological mechanisms that underlie changes in symptom severity (and age-related performance differences on laboratory measurements, e.g., Foxe et al., 2013) has the potential to address the influence of various interventions, normal maturation, parental involvement, and the host of other variables that might contribute to an optimal outcome.

Despite the challenges of conducting a prospective longitudinal study (attrition rates, significant time investment), the field of autism research is in a good position to follow children over time. With earlier age of diagnosis, an apparent increase in parents' interest in research, and the widespread use of instantaneous electronic communication, families may be easier to locate and more readily available for repeat visits. While diagnostic stability, social-communication skills, and response to intervention have been studied longitudinally (e.g., Anderson, D. K. et al., 2007; D'Elia et al., 2013; Gotham et al., 2012; Richler, Huerta, Bishop, & Lord, 2010; Rogers et
al., 2012), there are few longitudinal studies of neurophysiology in ASD. It is our responsibility, as researchers of a developmental disorder, to establish the long term relationships necessary to follow children from age of initial concerns (or beforehand in the case of high-risk infants) through adulthood.

Towards evidence-based treatments of sensory integration deficits. Sensory integration therapy, or occupational therapy with a sensory-based approach, is one of the widely used interventions for children with ASD. These therapies typically include playful activities involving swings, obstacle courses, brushing, weighted vests, ball pits, and more recently, interactive computerized programs. Sensory integration therapies typically provide the child with multiple sensory inputs and are thought to help organize the child's sensory system (Zimmer, M. & Desch, 2012). The use of sensory integration therapy as a treatment for ASD and for other populations has come under criticism in part because there is very little research on its efficacy (Zimmer, M. & Desch, 2012). A key challenge in conducting research on the efficacy of sensory integration is that the field lacks systematic outcome measures. Response to treatment is often evaluated in terms of the child's ability to participate in daily life activities and to meet the child's individualized goals. While these are certainly meaningful outcomes for children and their families they are not easily quantified in the way necessary to scientifically assess efficacy of treatment.

Since sensory integration therapy is intended to have an effect on the neurobiological integration of sensory information, which is presumed to be faulty in children with certain problematic behaviors (Schaaf & Miller, 2005), it is surprising that there are no published studies examining the brain mechanisms that may mediate behavioral outcomes. Now that we have established neurophysiological and behavioral metrics of sensory integration, we are in a
position to assess participants' responses to interventions aimed at improving sensory integration in ASD. In designing a study it is imperative that the treatment itself is standardized-- which in the field of sensory integration is uncommon because inherent in this approach is that the clinician uses his/her judgment to continuously adapt the environment and activities to the child's new abilities. Though a recent attempt was made to examine the feasibility and acceptability of a manualized protocol of clinician administered sensory integration therapy (Schaaf, Benevides, Kelly, & Mailloux-Maggio, 2012), continued development of this approach is needed before its efficacy can be properly assessed. Though a clinically administered therapy is preferred over a computerized intervention (particularly because face-to-face interactions are such an important component of any intervention aimed at helping individuals with social-communication deficits), computerized interventions based on sensory integration principles can be more easily evaluated empirically than traditional clinician administered sensory integration therapy. One such intervention is Auditory Integration Training (AIT) which "uses filtered and modulated frequencies imbedded in pleasant music to help re-train the auditory system and normalize the way the brain processes information" (Auditory Integration Training Services, http://www.aithelps.com/autism.php). According to the marketers, the benefits of AIT training for children with ASD include improvements in "sensory issues", speech and language, and social skills, as well as reductions in "self-stimming" and fewer "over-loads."

We can assess for neurophysiological changes associated with AIT (the independent variable) using a pre-post test design in which the dependent (outcome) measures are our established metrics of basic unisensory and multisensory processing (reaction times and ERPs) during the AVSRT task. To control for factors unrelated to AIT (e.g., repeated exposure to AVSRT, simple maturation over the intervening time period, etc.), it is important to have a
control group that does not receive AIT therapy. Significant changes in our behavioral or electrophysiological measures would provide preliminary evidence that AIT has an effect on the functioning of the nervous system. This is just one of the many approaches that we are now in the position to investigate as a basis for understanding and treating individuals with ASD.
REFERENCES


