BEHAVIORAL AND NEURAL INDICES OF AUDITORY TEMPORAL PROCESSING IN CHILDREN WITH AUTISM SPECTRUM DISORDERS

By

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CHAPTER I

Introduction

Autism spectrum disorders (ASD) form a continuum of neurodevelopmental disorders characterized by a triad of symptoms including pervasive deficits in social understanding and reciprocity, impairments in language and communication skills, and behavioral rigidity that includes repetitive behaviors and a preference for routines (American Psychiatric Association, 2000). Reports of both hypo- and hyper-arousal to sensory input, interest and preoccupation with sensory features of objects, and aversion or unusual reaction to specific sensory stimuli have been made consistently, starting with the original description of autism, and span across sensory modalities (e.g., vision, audition, touch) (Dawson & Watling, 2000; Kanner, 1943; O'Neill & Jones, 1997; Sigman & Capps, 1997). In fact, in response to the relatively ubiquitous presence of sensory abnormalities among individuals with ASD, this feature will be added to the diagnostic criteria for the disorder in the upcoming *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (Worley & Matson, 2012). In reviewing the literature on sensory dysfunction in ASD, Rogers and Ozonoff (2005) concluded that, in order to elucidate the nature of sensory abnormalities, future research should explore both behavioral and physiological responses to sensory stimuli across modalities. The current study seeks to address this charge by assessing and comparing psychophysical and electrophysiological responses to auditory input in children with and without ASD.

Auditory processing is targeted in this study given widespread clinical and parental reports of unusual responses to auditory input, as well as substantial experimental evidence

suggesting atypical auditory processing in individuals with ASD (Kellerman, Fan, & Gorman, 2005). A large majority of the experimental literature on auditory processing in ASD has explored responses to either complex language and speech input, or pitch changes among more acoustically simple stimuli (e.g., pure tones). Language processing impairments have been found consistently in ASD (Tager-Flusberg & Caronna, 2007), with deficits extending to syntactic, semantic, and pragmatic aspects of language (Rapin & Dunn, 2003), and also including failure to utilize prosodic cues in language (Paul, Augustyn, Klin, & Volkmar, 2005). In addition, atypical neural responses to speech sounds are among the most consistent basic auditory processing deficits reported in ASD (Jeste and Nelson, 2009; Kujala et al., 2013). For example, research has demonstrated delays in the brain response to speech sounds (Oram Cardy, Flagg, Roberts, & Roberts, 2005) and, moreover, that the degree of delay to both speech and non-speech sounds is related to the extent of language impairments in children with ASD (Oram Cardy, Flagg, Roberts, & Roberts, 2008; Roberts et al., 2011).

Regarding processing of non-speech stimuli, there is substantial evidence for intact behavioral performance on pitch-related tasks, at least among higher functioning individuals with ASD (Bonnel et al., 2010; Heaton, Hermelin, & Pring, 1998; Jones et al., 2009). Several neurophysiological studies, however, have revealed atypicalities in the neural correlates of pitch deviance detection (Jones et al., 2009; Tecchio et al., 2003). In contrast to findings related to pitch processing, literature related to processing of other physical properties of non-speech sounds has pointed to many areas of deficits for individuals with ASD (see Foss-Feig, Stone, & Wallace, 2012 for a review of these findings). For example, research has revealed abnormalities in the behavioral and neural responses to increasing stimulus intensity (Bruneau, Roux, Adrien, & Barthelemy, 1999; Khalfa et al., 2004), and individuals with ASD appear to have marked

difficulty in filtering competing auditory stimuli (Lepisto et al., 2009; Plaisted, Saksida, Alcantara, & Weisblatt, 2003). In addition, deficits in the encoding and perception of timing-related aspects of auditory stimuli (e.g., stimulus duration, interval between sequential stimuli) have also been reported in ASD (Lepisto et al., 2006; Oram Cardy, Flagg, Roberts, Brian, & Roberts, 2005; Orekhova et al., 2009). Clarifying deficits in the processing of temporal aspects of auditory stimuli among children with ASD is the focus of the current study.

Auditory Temporal Processing and Language Function

Rapid auditory temporal processing is critical for speech perception. The speech signal is a composite of sequential phonetic units (i.e., phonemes) that are uniquely characterized by their acoustic properties. The capacity to perceive rapid changes (i.e., on the order of milliseconds) in the acoustic signal is fundamental to the ability to accurately distinguish phonemes, which in turn allows parsing of meaningful speech from the stream of complex auditory information (Poldrack et al., 2001). The speech signal is marked by temporal cues including differing durations of specific sounds, occurrences of silent intervals, and rapid increases and decreases in amplitude. Perception of these temporal aspects of the speech signal allows detection of articulatory cues, discrimination of vowels versus consonants, differentiation of specific consonants, segmentation of syllables and words, and detection of prosodic cues (Rosen, 1992). Thus, the ability to accurately parse the stream of speech in order to perceive meaningful linguistic information is dependent upon intact auditory temporal processing.

The relation between rapid auditory temporal processing and language perception is further supported by functional neuroimaging studies, which point to left hemisphere lateralization for both functions. Left hemisphere dominance for language functioning has long

been reported, with speech perception most consistently localized within posterior regions of the left superior temporal cortex, with additional contributions from the left inferior frontal gyrus (i.e., Wernicke's and Broca's areas, respectively) (for review, Vigneau et al., 2006). Phonological processing, in particular, has also been shown to be subserved by left-hemisphere posterior temporal cortex, as well as by frontal regions in the left hemisphere (Poldrack et al., 2001; Zatorre, Meyer, Gjedde, & Evans, 1996). Parallel research has demonstrated that left-sided temporal and frontal regions are sensitive to rapid auditory processing demands for both speech- and non-speech stimuli (Belin et al., 1998; Fiez et al., 1995; Poldrack et al., 2001), and left-sided auditory cortex regions are preferentially activated during auditory gap detection (Zaehle, Wustenberg, Meyer, & Jancke, 2004). Finally, it has been reported that, in general, left hemisphere regions are more specialized for fine temporal resolution than are their right hemisphere analogs (Hammond, 1982).

Studies of other developmental disorders in which language functioning is impacted report temporal processing abnormalities, and hypothesize that these abnormalities may underlie core language-related difficulties (Farmer & Klein, 1995). Reading disabilities, such as dyslexia, are associated with phonological processing impairments (Wagner & Torgesen, 1987), and children with reading disabilities have demonstrated deficits on a wide range of tasks that assessed their rapid auditory temporal processing abilities (Tallal, 1980). In addition, during rapid presentation of non-speech acoustic stimuli, adults with dyslexia displayed reduced brain activation in left frontal regions (Temple et al., 2000). Similar rapid auditory temporal processing deficits have been reported in individuals with Specific Language Impairment (Tallal & Piercy, 1973; Wright et al., 1997), though there is more controversy in this population with regard to how primary temporal processing deficits may be for causing language-related deficits (Bishop

& Snowling, 2004). Overall, however, the link between rapid auditory processing and speech perception is well established, and research assessing clinical populations has demonstrated consistently that rapid auditory processing deficits are a contributing factor for language-related impairments.

Auditory Temporal Processing in ASD

A similar role for temporal processing abnormalities can be envisioned in ASD, as language is often impaired, and communication deficits are central to the ASD diagnosis. Along these lines, theoretical models have suggested abnormalities in the "temporal binding" of input within and across sensory modalities (Brock, Brown, Boucher, & Rippon, 2002). This phenomenon refers to the tight temporal correlational of brain activity across regions responding to a stimulus, and is thought to enable integration of input and responses to support complex perception. Thus, some have proposed temporal binding deficits might underlie impaired perception of complex stimuli as well as aberrant information processing in ASD. More recently, Allman (2011) posited that abnormalities in processing of temporal information more broadly could underlie many of the core symptoms of ASD, citing evidence of impaired time perception, reduced temporal binding, and difficulties with time-related concepts (e.g., past/future, sequence). In general, given that we live in a dynamic world, impairment in the capacity to resolve and respond to rapidly presented information could have broad implications not only for sensory functioning, but also for higher order communication, social, and perceptual functions.

Despite these factors, the capacity to accurately process temporal aspects of auditory stimuli has received minimal attention in ASD. However, the available literature on this topic has identified abnormalities in the processing of timing information both *within* individual stimuli

and *between* sequential stimuli presented in rapid succession. Specifically, children with ASD have shown difficulties replicating tones of standardized durations ranging from one to five seconds (Szelag, Kowalska, Galkowski, & Poppel, 2004), as well as reduced detection of duration deviance, indexed by both behavioral and electrophysiological methods (Lepisto et al., 2006). Further, they have shown impaired ability to determine the temporal order of auditory stimuli presented in rapid sequence (Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2011), and reductions in their neural response to simple tones separated by short temporal intervals (Oram Cardy, Flagg, Roberts, & Roberts, 2005). Finally, delays in the neural response to repeated pure tone stimuli also suggest abnormalities in the temporal encoding of simple auditory input among children with ASD (Roberts et al., 2010). Together, these findings converge in suggesting deficits in rapid auditory temporal processing in children diagnosed with ASD, yet much work remains to be done.

The Current Study

This study targeted temporal aspects of auditory processing, as they are among the most understudied elements of sensory processing, yet possess widespread implications if their processing is impaired. In particular, the current study followed up on previous findings demonstrating an increased temporal order judgment threshold in children with ASD (Kwakye et al., 2011), by using a classic gap detection paradigm. This paradigm measures the minimum interval between sequential stimuli that is needed for individuals to perceive an interruption between the stimuli (i.e., identify that they are discontinuous, rather than a single, continuous sound). Our previous findings of increased threshold for resolving presentation order among auditory stimuli in ASD (i.e., indicating that children with ASD require longer time intervals

between paired auditory stimuli to resolve their temporal order than do children with typical development [TD]) suggest abnormalities in basic temporal processing tapped by gap detection tasks. However, they could also be interpreted as reflecting deficits in higher-order cognitive processes, rather than more basic auditory temporal resolution. In other words, it remains to be clarified whether our previous results reflected impairment in the *perceptual* ability to detect small gaps between stimuli, or whether children with ASD were in fact equally able to resolve these gaps between stimuli at a perceptual level, but had difficulty with the more complex and cognitively-demanding *order judgment* aspect of the task. Either scenario could explain group differences seen in our auditory temporal order judgment task; thus, this study was initiated based on the idea that use of a more simple gap detection task would be helpful in clarifying the level at which auditory temporal processing goes awry in ASD.

Gap detection thresholds have been shown to be impaired in disorders characterized by language processing deficits (e.g., dyslexia). Thus, given the centrality of language and communication deficits in ASD, one might expect similar impairments in this disorder as well. The ability to detect gaps between stimuli is reliant on both the capacity to encode temporal intervals, as well as the timing of neuronal response and recovery. Therefore, in the set of studies described here, we first examined the absolute threshold (i.e., just noticeable difference) at which children with ASD, compared to those with TD, could detect silent gaps within broadband auditory stimuli, for which gap detection thresholds are typically at their lowest, between 2 and 3 milliseconds (Formby & Muir, 1989). Additionally, to clarify the extent to which experimental findings relate to the everyday experiences of children with ASD, the first study also explored relations between psychophysical findings, parental report of sensory symptoms and social communication deficits, and standardized assessment of language abilities that might be

impacted by underlying auditory temporal processing alterations. In parallel, we examined the neural response to a set of fixed gap intervals both above and below behavioral detection thresholds. In this way, we aimed to evaluate whether gap detection is impaired in ASD, as well as whether the neural correlates of gap detection differ in children diagnosed with ASD relative to their age- and IQ-matched typically developing peers.

Specific Aims

Aim 1. To measure gap detection thresholds using psychophysical procedures with children with autism spectrum disorders (ASD) and typical development (TD) in order to assess the integrity of rapid auditory temporal processing in ASD. (CHAPTER 2; Study I).

Aim 2. To explore the relation between individual differences in rapid auditory temporal processing (as indexed by gap detection thresholds from Aim 1), and degree of social, communication, and sensory symptoms in children with ASD, as well as phonological language processing abilities in these children. (CHAPTER 2; Study I).

Aim 3. To characterize, using electrophysiological methods, early temporal aspects of the neural response to barely-detectable gaps in auditory stimuli, in children with and without ASD. (CHAPTER 3; Study II).

CHAPTER II

Study I

The first goal of Study I was to measure gap detection thresholds using psychophysical procedures in children with autism spectrum disorders (ASD) and typical development (TD), in order to determine the integrity of rapid auditory temporal processes in ASD. Here, rapid temporal processing is defined as the ability to detect brief temporal events (i.e., silent gaps) within auditory stimuli. The second goal of Study I was to explore the relation between individual differences in rapid auditory temporal processing (as indexed by gap detection thresholds) and degree of social, communication, and sensory symptoms in children with ASD, as well as phonological language processing abilities in these children. Only children with ASD were included in analyses associated with this second aim, as it was designed to explore the clinical implications of any differences identified with the psychophysical task. The following hypotheses were tested:

Hypotheses

Hypothesis 1. Children with ASD will show deficits in auditory temporal processing relative to children with TD. In particular, they will have more difficulty detecting brief silent gaps in noise, reflected in higher gap detection thresholds determined by a psychophysical staircase procedure.

Hypothesis 2. Among children with ASD, greater alterations in rapid temporal processing, as measured by psychophysical procedures, will be associated with greater impairments in social functioning, receptive language, and phonological processing, as well as higher levels of auditory sensory abnormalities, as indexed by parent report and direct clinical assessment.

Method

Participants. This study included 24 children diagnosed with ASD and 27 children with TD, all between 10 and 13 years of age. An additional four participants with ASD were enrolled in this study, but were unable to complete psychophysical task procedures successfully; thus, their data were excluded from study analyses. All participants had: (a) normal or corrected-to-normal vision and hearing; (b) intact cognitive skills (i.e., IQ > 70); and, (c) absence of genetic or neurological disorders, history of seizures, or past head injury. Children with ASD had received previous diagnoses of Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS). For this study, diagnoses were confirmed with the Autism Diagnostic Observation Schedule (Lord et al., 2000) and Autism Diagnostic Interview-Revised (Lord, Rutter, & Le Couteur, 1994); all participants in the ASD group met diagnostic criteria on both measures. Children with TD had no family history of ASD in first- or second-degree relatives and no current or past diagnosis of any neurological, learning, or psychological disorder (e.g., seizures, ADHD, anxiety, depression). All scored below the at-risk cutoff on the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003), a screening questionnaire for ASD diagnostic risk. Participants with ASD and TD were matched for age, gender, handedness, and IQ score, as measured by the Wechsler Abbreviated Scales of

Intelligence (Weschsler, 1999) (Table 1). All participants passed pure tone audiometric hearing screenings, and were able to detect 500, 1000, 2000, and 4000 Hz tones at 20 dB in both ears.

Table 1
Study I Participant Demographics

Variable	**Group Means**		**Statistics**	
	ASD	**TD**	**statistic**	***p*-value**
Age (years)	11.94 ± 1.3	11.93 ± 1.3	t = 0.02	0.99
Full Scale IQ	115.96 ± 17.4	114.50 ± 12.9	t = -0.32	0.75
Handedness[a]	18 R; 5 L	21 R; 2 L	$\chi^2 = 1.52$	0.21
Gender	21 M; 3 F	23 M; 4 F	$\chi^2 = 0.06$	0.57

[a] Handedness information missing for 1 child with ASD and 4 children with TD

Procedure. Children with ASD (i.e., Autistic Disorder, Asperger's Disorder or PDD-NOS) and TD were recruited by: (a) sending emails and/or making phone calls to the families of children who had participated in previous research studies conducted within the Treatment and Research Institute for Autism Spectrum Disorders (TRIAD) or other programs at Vanderbilt University, and had signed consent to be contacted for future research; (b) distributing flyers at community seminars and meetings; and (c) sending a broadcast email to the Vanderbilt University Medical Center listserver. Potential participants whose parents expressed interest in having their child participate in the study were initially screened for eligibility using a phone interview. Families who were eligible according to this initial phone screening, continued to express interest, and were available for participation were subsequently enrolled.

Participants completed all clinical characterization, hearing screening, and psychophysical procedures in one to two visits, depending on the preferences of families, the

needs of each child, and how many assessments were to be completed. For example, as part of the study, adequate cognitive functioning for inclusion was ensured for all participants (i.e., by Full Scale IQ score above 70) and diagnosis was confirmed for participants with ASD (i.e., with recent ADOS and ADI-R scores above cutoff). However, cognitive and diagnostic assessments were not conducted if children had completed similar testing in the past year and their parents could provide the scores; thus, some participants required fewer or shorter testing sessions. Sessions typically lasted between two and three hours. Parents of all participants gave informed consent, and all children in both groups gave assent prior to participation in any component of this study. All children received compensation for their participation at each visit. Procedures were approved by the Vanderbilt University Institutional Review Board.

Study participation included children's completion of: (a) a clinical assessment battery evaluating cognitive and language functioning, with testing administered by an advanced graduate student and/or a trained research assistant; (b) a psychophysical task assessing gap detection thresholds; and (c) a brief hearing screening using behavioral audiometry. In addition, parents of all children completed electronic questionnaires and rating forms as part of their child's participation. For children with ASD without recent diagnostic assessments, participation included a direct diagnostic assessment of ASD (i.e., with the ADOS) and a parent interview targeting current and historical symptoms of the disorder (i.e., with the ADI-R). Diagnostic assessments were completed by a trained, research-reliable, advanced doctoral student in clinical psychology, under the supervision of a licensed psychologist.

For the psychophysical procedures, participants sat in a light- and sound-attenuated room in front of a computer monitor, which was centered between two speakers. Auditory stimuli were presented via these external speakers and children were seated centered between the two

speakers in order to ensure auditory stimuli were of equal binaural amplitude. Visual fixation and cues guiding participants regarding task progress were presented in white text against a black background on a PC monitor (NEC Multisync FE992, 22 inch screen; 150 Hz refresh rate; 640x480 pixel resolution). Volume of auditory stimuli was constant (and well above hearing threshold; 80 dB) across participants. Stimuli were presented using PsychToolbox (www.psychtoolbox.org) within Matlab (MathWorks, Natick MA). Participants indicated their responses to task stimuli on an "X-keys" serial response box, which recorded responses through the PsychToolbox within Matlab. Throughout the experiment, participants were monitored via a closed-circuit video camera and, when necessary, a researcher remained in the room to cue on-task behaviors. Participants were allowed to take a break between blocks and additional breaks were given mid-block as needed.

Measures. Children participated in a series of cognitive, diagnostic, and language-related assessments. In addition, parents completed a series of rating scales to report on their child's social, communication, and sensory fuctioning, as well as questionnaires regarding demographics and their child's neurological history.

Cognitive assessment. The Wechsler Abbreviated Scale of Intelligence (Weschsler, 1999) was administered to all participants. The WASI includes two verbal and two non-verbal subtests, yielding standard score estimates of Verbal, Non-Verbal and Full Scale IQ (Mean = 100, SD = 15). The WASI was administered to confirm verbal and non-verbal IQ scores above 70 for children in both groups. This cutoff was chosen to increase the likelihood of participants' ability to comprehend and follow task instructions, to provide accurate behavioral response, and to sustain on-task behavior over the course of experimental procedures. WASI scores were also used to ensure that the ASD and TD groups were matched for cognitive ability.

Diagnostic assessments. For children in the ASD group, the presence of an autism spectrum diagnosis was confirmed using gold-standard assessment procedures: the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), the Autism Diagnostic Interview – Revised (ADI-R; Lord et al., 1994), and a clinical diagnosis. All children were required to meet ADOS and ADI-R criteria for ASD, defined by exceeding the cutoff scores on both measures. Clinical diagnosis was made using DSM-IV-TR criteria (American Psychiatric Association, 2000), according to the clinical judgment of an advanced doctoral student in clinical psychology with expertise in autism spectrum disorders, under the supervision of a licensed clinical psychologist.

The ADOS provides a semi-structured context in which a trained, research-reliable examiner assesses a child's social interaction, communication skills, and behavioral patterns. The examiner then rates the child on a series of items, which combine to give algorithm scores for Social Affect and Repetitive Behavior domains (Gotham, Risi, Pickles, & Lord, 2007). The Social Affect and Repetitive Behavior domain scores are combined to yield a Total Score, for which "at-risk" cutoffs for ASD and autism are provided. All children in this sample were assessed with the Module 3 version of the ADOS, which is designed for children with fluent speech. Summed across Language and Communication, Reciprocal Social Interaction, and Restricted and Repetitive Behaviors algorithm items, total scores can range from 0 to 28. For the Module 3, the autism spectrum cutoff score is 7 and the autism cutoff score is 9.

The ADI-R is a semi-structured interview, which was administered to parents of children with ASD by a trained, research reliable examiner. The ADI-R inquires about current functioning and historical concerns within the three core impairment domains associated with an ASD diagnosis (i.e., language and communication, reciprocal social interactions, restricted and

repetitive behaviors). The examiner rates parent responses to each item according to preset codes, and individual item scores are combined according to algorithms associated with each domain. Total scores within each ADI-R domain are then compared to "at-risk" cutoff scores for ASD. Scores on the Reciprocal Social Interaction domain range from 0 to 30, with an at-risk cutoff score of 10. In the Communication domain, algorithm scores can range from 0 to 26, with scores at or above 8 meeting the at-risk cutoff. Finally, in the Restricted Repetitive Behaviors domain, scores range from 0 to 12, and the at-risk cutoff score is 3.

Social assessments. ADOS and ADI-R scores from the diagnostic assessment were used to relate experimental indices of auditory temporal processing to core ASD symptoms among children with ASD. Specifically, the Total Score from the ADOS and the three domain scores from the ADI-R were used for this purpose. Parents of children in both groups completed the 40-item Social Communication Questionnaire (SCQ; Rutter et al., 2003), which measures ASD-related symptoms with content similar to that of the ADI-R, but using questionnaire rather than interview format. The SCQ was used to provide a continuous measure of autism symptomatology across both groups. The SCQ is a 40-item questionnaire, and SCQ scores can range from 0 to 40. Given that it also has a cutoff score (i.e., 15) above which scores are considered indicative of high risk for ASD, the SCQ also served as a brief screening to ensure that none of the control participants were at risk for an ASD diagnosis (i.e., that all had SCQ scores below the at-risk cutoff).

In addition, parents of children in both groups completed the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005), a 65-item questionnaire designed to measure ASD-related symptoms as viewed in everyday social environments. The SRS generates five subscale scores, related to Social Awareness, Social Cognition, Social Communication, Social

Motivation, and Autistic Mannerisms. Scores across the five subscales combine to yield a Total Score. All subscales and the combined total provide T-scores (M = 50, SD = 10) in relation to children of the same gender from the normative sample. However, because T-scores are not computed based on age norms, raw SRS scores were utilized to increase the range and score variability among participants. For the Total Score on the SRS, scores can range from 0 to 195.

Sensory assessments. Parents of children in both groups completed the Sensory Profile (SP; Dunn, 1999), a 125-item questionnaire that yields section and factor scores (e.g., auditory, visual, multisensory processing, sensory sensitivity, and sensory seeking) related to sensory symptoms and atypical sensory experiences. Raw scores are totaled for each factor and section, with lower scores on scales indicating greater sensory abnormalities. For this study, the Auditory section score, which is derived from 8 questions, was targeted. Scores on this scale can range from 8 to 40. Scores below 29 are associated with probable difference from the norm; those below 26 are considered "definitely different" from the norm.

In addition, parents completed the Sensory Experiences Questionnaire (SEQ; Baranek, David, Poe, Stone, & Watson, 2006), which inquires about unusual sensory interests and aversions specifically relevant to ASD. The SEQ includes 43 items, which are categorized as reflecting hypo-responsive and hyper-responsive patterns of responding to sensory stimuli. Subscales can be further divided into social and non-social items, or into items specific to individual sensory modalities. The total score across all Auditory items (n = 6) was of interest for this study. Scores on this scale can range from 6 to 30, with higher scores indicative of more significant auditory symptoms.

The SP and SEQ were used to evaluate the extent to which our experimental data regarding the integrity of auditory processing in ASD relates to auditory sensory behaviors observed in naturalistic settings.

Language assessments. Children in both groups completed select subtests from the Comprehensive Test of Phonological Processing (CTOPP; Wagner, Torgesen, & Rashotte, 1999) and the Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4; Semel, Wiig, & Secord, 2003) in order to assess phonological processing abilities and language comprehension. Both measures are standardized, norm-referenced assessments that were administered to children by a trained examiner. The CELF-4 also includes caregiver report questionnaires, which were administered to parents at the time of their child's participation.

The CTOPP assesses phonological awareness, phonological memory, and rapid naming. The measure comprises subtests including Elision, Blending Words and Non-Words, Segmenting Words and Non-Words, Phoneme Reversal, Non-Word Repetition, Memory for Digits, and Rapid Digit and Letter Naming. Subtests yield scaled scores (Mean = 10, SD = 3) and combine to form three quotient scores (i.e., Phonological Awareness, Phonological Memory, Rapid Naming), each with a mean of 100 and a standard deviation of 15.

The CELF-4 Sentence Repetition, Concepts and Following Directions, and Word Classes – Expressive and Receptive subtests were administered to all children. Subtests typically yield scaled scores with a mean of 10 and a standard deviation of 3; however, because subtest norms do not extend for use with the oldest children in this study sample, total raw scores for each subtest were used for analyses that included the CELF-4 measures. Raw scores can range from 0 to 96 on the Sentence Repetition subtest, from 0 to 54 on the Concepts and Following Directions subtest, and from 0 to 48 on the Word Classes – Expressive and Receptive subtest total

(including ranging from 0 to 24 for separate Expressive and Receptive components of this subtest).

Finally, parents completed two rating scales from the CELF-4: the Observational Rating Scale (ORS), which inquires about language use in everyday contexts, and the Pragmatics Profile, which evaluates pragmatic language functioning. The CELF-4 ORS is a 40-item questionnaire that subdivides items into Listening, Speaking, Reading, and Writing domains. For the purpose of this study, analyses focused on the Listening domain, as it seemed most relevant given our focus on auditory processing. The Listening domain consists of nine items, with possible scores ranging from 9 to 36; higher scores are associated with greater language-related difficulties.

The CELF-4 Pragmatics Profile is a 52-item rating form, which categorizes items into three categories: Rituals and Conversation Skills; Asking for, Giving, and Responding to Information; and Nonverbal Communication. For the purposes of this study, the Total Score across all items on the CELF-4 Pragmatics Profile was targeted. Total Scores can range from 52 to 208, with lower scores indicative of worse pragmatic language abilities. For 10-12 year old children, scores below 136 are considered to reflect clinically relevant impairment; for children 13 years and older, the cutoff score for clinically significant pragmatic impairments is 142.

The CTOPP and CELF-4 measures were used to quantify participants' language-related skills in order to examine whether a relation could be detected between experimental measures of rapid auditory processing and more clinically relevant markers of language functioning and phonological processing among children with ASD.

Demographic information and neurological history. In addition to clinical data, demographic information was collected including child's age, grade, race, and ethnicity.

Additional demographic data collected included parents' current marital status, level of education, income, and work status, as well as siblings' age, gender, and diagnoses (if any). Handedness was reported by parents, and was also determined using an experimenter-administered questionnaire completed directly with each child. Finally, neurological history, including information regarding any previous concussions, seizure activity, etc. was collected in order to ensure initial screening had effectively excluded participants with notable neurological histories. As part of this form, parents also reported on whether their children were prescribed any psychotropic medications.

Hearing screening. Hearing thresholds were screened using a standard clinical audiometer. Participants wore noise-canceling headphones, through which pure tone stimuli of 500, 1000, 2000, and 4000 Hz were presented at 20 dB. At each of the four frequency levels, two trials were presented to each ear, resulting in a total of 16 trials. Participants were asked to raise one hand each time they heard a tone. If participants failed to respond to either of the two trials per ear and frequency, a third trial at that ear and frequency level was administered. Exact hearing thresholds were not computed, but all participants passed screening procedures (i.e., responded correctly on 2 of 2 [or 2 of 3] trials for each frequency, in each ear), and thus were eligible for participation in remaining procedures associated with this study.

Psychophysical task. Psychophysical procedures were used to determine gap detection thresholds in the auditory modality. Specifically, the QUEST procedure was implemented through PsychToolbox (www.psychtoolbox.org) within Matlab (MathWorks, Natick MA). QUEST is an adaptive staircase procedure that utilizes Bayesian theory and estimates a psychometric function for each trial, using information from the previous trial to select a new stimulus value for the subsequent trial, and ultimately converging on a final performance level

that represents an individual's psychophysical threshold (Watson & Pelli, 1983). For this experiment, the threshold performance level was set to 85% accuracy. The parameter varied by the QUEST procedure was the duration of the silent gap within sequential trials. In other words, the QUEST procedure was used to determine the minimum gap size for which a given participant could detect the presence of the silent gap with 85% accuracy. Two blocks of two interleaved staircases, each containing 26 trials, were completed by each participant. Thus, each block contained 52 trials total. Participants were offered a break in between blocks. The starting gap size was 4.5ms for both staircases within the first block; starting gap sizes for staircases in the second block were determined based on the output from the staircases in the preceding block.

Auditory stimuli consisted of white noise bursts created in Adobe Audition (Adobe Systems, Mountain View, CA, USA) at a sampling rate of 44100 Hz. White noise stimuli were selected because they are associated with the lowest gap detection thresholds (Shailer & Moore, 1987) and because they allowed for more precision and control of gap intervals with fewer irrelevant auditory cues (e.g., ramping, background masking noise). Stimuli were 1000ms in total duration. Within stimuli containing gaps, intervals of silence ranged from 0.5ms to 100ms, and were centered relative to the overall stimulus duration.

A two-interval, forced choice (2IFC) gap detection procedure was used. This method was selected because it is relatively unbiased compared to yes/no procedures (i.e., where participants simply indicate whether or not they perceived a gap in a single auditory stimulus per trial) (Green & Swets, 1966). Specifically, by asking participants to report *in which* stimulus interval they detected the gap, rather than *whether* they detected the gap, use of the 2IFC procedure enabled us to reduce potential effect of response bias (e.g., tendency to be more or less conservative in indicating detection of near-threshold gaps), which could theoretically also differ

as a function of group, on the perceptual thresholds computed by psychophysical procedures (Macmillan & Creelman, 2005). Thus, for each trial, participants were presented with a pair of stimuli, one continuous and the second containing a gap. Each trial began with a 1000ms visual fixation, presented on a high refresh rate PC monitor. Fixation was followed by onset of the pair of auditory stimuli, then by presentation of a visual response cue (i.e., question mark on the computer screen) and a 3000ms response window, which terminated following button press response. If participants did not respond within 3000ms, a trial repeated itself with the same gap size and interval location. Within trials, paired stimuli were separated by 1000ms. Inter-trial interval varied randomly between 800 and 1300ms, beginning after the button press response associated with the preceding trial. Stimulus presentation was controlled by Matlab.

For each trial, participants were asked to make a forced choice decision as to which interval contained the gap (i.e., the first or the second) and to indicate their response via a hand-held button box. Gap presentation occurred in the first interval on 50% of trials overall, but which of the two intervals the gap was presented in was randomly selected for each trial. Prior to completing the primary task, participants were administered four practice trials that provided auditory feedback regarding accuracy, in order to confirm task comprehension prior to participants' beginning the full task. Additional repetition of instructions and practice trials were provided to participants as needed. All participants included in this sample responded correctly to at least three of four practice trials prior to beginning the task. The full task provided no further feedback for accuracy. Buttons (i.e., left or right) corresponding to the first and second interval were counter-balanced across participants.

Data analysis.

Psychophysical data preparation. Psychophysical threshold procedures yielded four threshold estimates (i.e., one from each of the two interleaved staircases, in both the first and second blocks) for each participant, reported in milliseconds. Because QUEST procedures estimate thresholds in the log space, the log of each threshold was computed and these four values were averaged. This average was then transformed back to milliseconds (i.e., by computing 10^average_threshold) to yield a single value that represented the auditory gap detection threshold for each participant. Gap detection thresholds indicated the minimum gap size [in milliseconds] at which participants could detect the presence of a gap with 85% accuracy.

Analytic plan: Hypothesis 1. In order to evaluate whether group differences exist in auditory gap detection thresholds, independent-sample *t*-tests were computed with group as the independent variable and mean gap detection threshold as the dependent variable.

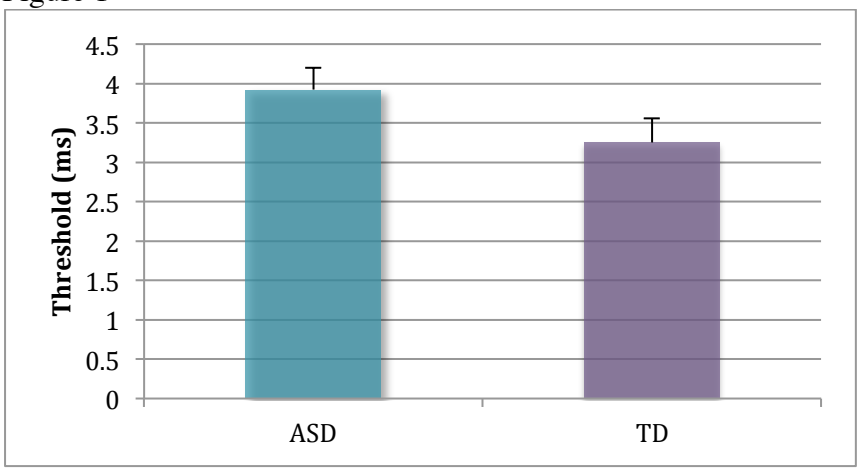
Analytic plan: Hypothesis 2. In order to evaluate whether auditory gap detection abilities were related to clinical symptoms in the ASD group, bivariate correlations were conducted between gap detection thresholds and a number of clinical variables. In order to reduce the number of correlations conducted (i.e., to help control for Type I error), for clinical measures yielding summary and/or total scores (i.e., ADOS, ADI-R, Social Communication Questionnaire, Social Responsiveness Scale, CELF-4 Pragmatics Profile), correlations were first conducted between thresholds and summary scores. Additional analyses using individual subtest or subdomain scores were conducted only when summary scores were significantly correlated with gap detection threshold. For both the Sensory Profile and the Sensory Experiences Questionnaire, correlations were only conducted with the Auditory subdomain scores, as these

were conceptually most relevant for the current study. For the CELF-4 Observational Rating Scale, the Listening domain was the focus of correlational analyses. Correlations were conducted with each CELF-4 subtest from the direct assessment battery, as no overall index score was available to capture every subtest administered to all participants. Finally, individual CTOPP subtest scores were included in correlational analyses, since phonological processing abilities were most likely to be related to gap detection thresholds based on findings from studies in other clinical populations.

Results

Psychophysical thresholds. Results of QUEST procedures indicated that the auditory gap detection threshold for children with ASD was 3.92ms ± 1.36, whereas the threshold for children with TD was 3.25ms ± 0.66 (Figure 1). In other words, on average, children with ASD required silent gaps 3.92ms in length in order to reliably detect that a gap had occurred in a stimulus, whereas, on average, children with TD could reliably detect the presence of a silent gap when it was only 3.25ms in length. This difference is statistically significant, $t(49) = 2.28$, $p = 0.027$, Cohen's $d = 0.663$, indicating that auditory gap detection thresholds are substantially higher in children with ASD. Thus, children with ASD require significantly longer silent gaps in noise to reliably detect the gaps' presence. The difference between groups reflects a 20.6% increase in gap detection threshold in children with ASD, relative to those with TD.

Figure 1



Auditory Gap Detection Thresholds in Children with ASD and TD.

Relations with clinical variables. Among children with ASD, correlations were conducted to relate auditory gap detection thresholds with parent report and direct assessment measures of sensory, social, and language functioning. Specifically, correlations were conducted between auditory gap detection threshold and: auditory domain scores from the Sensory Profile and Sensory Experiences Questionnaire; the ADOS Total Score; the three ADI-R core domain algorithm scores; the CELF-4 Observational Rating Scale Listening Domain score; and total scores from the Social Communication Questionnaire, Social Responsive Scale, and CELF-4 Pragmatics Profile. Correlations were also conducted with subtest scores from the CTOPP and CELF-4 direct assessment measures of language functioning, as well as with Verbal IQ scores from the WASI. For most measures, data were missing from a small number of, largely due to parents' not completing all questionnaires at the time of their appointments, and failing to return completed questionnaires afterward, despite repeated attempts to follow up. Means, standard deviations, and ranges for all clinical variables are presented in Table 2. The number of participants with ASD for whom data were available for each measure is also reported.

Table 2
Descriptive Information for Clinical Variables among ASD Participants

Clinical Measure	n	Mean	SD	Study Range
Social Communication Questionnaire Total Score	20	18.12	9.07	6-36
Social Responsiveness Scale Total Raw Score	19	95.45	27.03	54-138
Sensory Profile – Auditory Domain Score	18	24.18	5.72	13-34
SEQ – Auditory Domain Score	21	16.05	3.94	8-22
CELF-4 ORS – Listening Domain Total Score	19	21.32	5.01	11-32
CELF-4 Pragmatic Profile Total Score	20	126.77	21.32	100-203
ADOS Algorithm Total Score	24	13.71	3.86	8-24
ADI-R Reciprocal Social Domain Total Score	22	16.82	6.42	8-30
ADI-R Communication Domain Total Score	22	14.09	4.66	6-26
ADI-R Repetitive Behavior Domain Total Score	22	6.23	2.14	3-11
CELF-4 Concepts and Following Directions Raw Score	23	49.83	4.04	38-54
CELF-4 Recalling Sentences Raw Score	23	68.70	13.27	37-89
CELF-4 Word Classes Receptive Raw Score	24	16.33	5.04	8-24
CELF-4 Word Classes Expressive Raw Score	24	12.88	4.79	6-22
CTOPP Elision Subtest Scaled Score	24	11.37	1.84	6-13
CTOPP Blending Words Subtest Scaled Score	24	11.42	2.57	6-15
CTOPP Rapid Digit Naming Subtest Scaled Score	24	9.29	2.99	5-15
CTOPP Non-word Repetition Subtest Scaled Score	24	10.92	2.50	5-15
CTOPP Rapid Letter Naming Subtest Scaled Score	24	8.79	3.16	3-16
CTOPP Memory for Digits Scaled Score	24	9.58	3.06	5-16

Regarding sensory functioning, no significant relations were seen with the auditory domains from either the Sensory Profile, $r(18) = -0.319$, $p = 0.20$, or the Sensory Experiences Questionnaire, $r(21) = 0.112$, $p = 0.61$. Auditory gap detection thresholds also were not correlated with diagnostic features of ASD, as indexed by direct assessment according to the ADOS Total Score, $r(24) = 0.249$, $p = 0.24$, or parent report on any of the ADI-R core domains (all rs < 0.16, all ps > 0.48), the Social Communication Questionnaire total score, $r(20) = 0.030$,

$p = 0.90$, or the Social Responsiveness Scale total score, $r(19) = 0.031$, $p = 0.90$. Finally, thresholds were not correlated with parent report of pragmatic language functioning on the CELF-4 Pragmatics Profile, $r(20) = -0.054$, $p = 0.82$.

However, auditory gap detection thresholds were correlated with several aspects of language functioning, as measured by direct assessment. A statistically significant relation with the Blending Words subtest of the CTOPP was found, $r(24) = -0.440$, $p = 0.031$, suggesting a relation between gap detection abilities and aspects of phonological processing in children with ASD. Auditory gap detection abilities were also correlated with receptive and expressive language abilities, as assessed with the CELF-4. Specifically, thresholds were correlated significantly with raw scores from the Concepts and Following Directions subtest, $r(23) = -0.411$, $p = 0.046$, the Word Classes – Receptive subtest, $r(24) = -0.668$, $p < 0.001$, and the Word Classes – Expressive subtest, $r(24) = -0.489$, $p = 0.015$. A trend for a relation between gap detection threshold and the CELF-4 Recalling Sentences subtest score, $r(23) = -0.367$, $p = 0.085$, was also detected. Finally, analyses revealed a trend for a relation between auditory gap detection threshold and complex verbal reasoning and expression abilities, as indexed with the WASI Verbal IQ score, $r(23) = -0.353$, $p = 0.099$.

Discussion

Results of this study revealed increased auditory gap detection thresholds in high-functioning children with ASD, relative to those with TD, indicating impairment in rapid auditory temporal processing in this population. This finding is consistent with previous findings from our group, wherein children with ASD displayed increased auditory temporal order judgment thresholds relative to their typically developing peers (Kwakye et al., 2011). The

present finding extends the previous one by revealing similar deficits in a simpler task requiring less complex perceptual judgments (i.e., detection of the presence/absence of a gap versus determination of the presentation order of sequential stimuli). More broadly, it provides additional support for a temporal processing deficit for auditory information in ASD.

Comparison with other findings related to auditory temporal processing in ASD. The present finding is consistent with results from Bhatara, Babikian, Laugeson, Tachdjian, and Sininger (2013), who also reported increased gap detection thresholds in ASD. Bhatara and colleagues noted particular difficulty detecting gaps in pure tone stimuli, with gap detection deficits less prominent for wide-band white noise (2000-14000Hz). In the present study, we used only white noise stimuli, and identified differences for these stimuli as well. Bhatara and colleagues demonstrated that gap detection threshold in children with ASD was significantly related to speech in noise perception, providing evidence in support of our notion that rapid temporal processing deficits in ASD could underlie difficulties with speech perception and, as a result, communication more broadly. The correlational finding from Bhatara et al. also parallels our correlational results, wherein impaired auditory gap detection was associated with greater phonological and receptive language processing deficits in children with ASD.

The magnitude of difference in gap detection threshold between groups was quite a bit smaller in the present study than in the Bhatara et al. study (i.e., 20% higher vs. 100% higher in the two studies, respectively), even when only examining results for white noise stimuli in the latter study. Methodological differences between our study and that of Bhatara and colleagues may have affected the magnitude of results. For example, whereas in the current study we used a two-interval forced choice procedure, Bhatara and colleagues used a three-alternative forced choice procedure that placed higher demands on working memory. In addition, the previous

study relied on pairing auditory stimuli with visual prompts to cue responding, whereas our study did not utilize cross-modal pairing. Moreover, the previous study provided feedback after each trial, and used large initial gap size (50ms). In the present study we only provided feedback during practice trials and the initial gap size was closer to threshold (i.e., 4.5ms). Thus, the present study may reflect gap detection threshold values in ASD that are closer to "true" values, as we used a simpler task that more directly assessed perception while avoiding including extra task parameters or tapping extraneous cognitive processes (e.g., cross-modal response cueing, responsiveness to feedback, working memory) that could differentially affect children with ASD, thereby confounding study results. Nonetheless, the results of our study and that of Bhatara and colleagues are consistent in their directionality, and concur in revealing impaired auditory gap detection abilities in ASD.

Our findings are also generally consistent with other behavioral studies assessing the ability of individuals with ASD to process timing information in auditory stimuli. Children with ASD have been shown to have difficulty reproducing pure tone auditory stimuli of standard durations. This deficit becomes more prominent with increasing stimulus duration, and is characterized by less accurate and more variable reproductions produced by children with ASD (Martin, Poirier, & Bowler, 2010; Szelag et al., 2004). Some studies have shown differences in temporal interval sensitivity (i.e., comparing auditory stimuli of various durations to a standard duration). Specifically, when asked whether probe durations were the same or different than standard durations, individuals with ASD showed reduced temporal sensitivity for auditory stimuli (Falter, Noreika, Wearden, & Bailey, 2012). However, in two studies that asked whether probe durations were shorter or longer than standard durations (i.e., as opposed to the same/different judgment required by Falter et al.), Jones et al. (2009) and Mostofsky, Goldberg,

Landa, and Denkla (2000) did not find deficits in duration sensitivity in children and adolescents with ASD. Notably, a lack of group differences was observed during comparisons both of pure tone stimuli (Jones et al., 2009), and of silent intervals demarcated by brief tones on either end (Mostofsky et al., 2000). Therefore, stimulus properties and specific perceptual judgments asked of participants may affect the degree to which auditory temporal processing deficits are observed in ASD.

More consistent findings have been reported in auditory temporal processing tasks that target shorter durations. For example, in a brief behavioral assessment associated with an electrophysiological task, Lepisto et al. (2006) reported that children (though not adults; Lepisto, Nieminen-von Wendt, von Wendt, Naatanen, & Kujala, 2007) with Asperger's Disorder were less reliable than their TD counterparts in their ability to detect differences between standard and probe stimulus durations when the standard duration was 190ms. Our previous temporal order judgment findings are in line with the notion that resolving temporal information in auditory stimuli may be particularly impacted in ASD for stimuli of short durations (Kwakye et al., 2011). In addition, findings from Alcantara, Cope, Cope, and Weisblatt (2012) noted atypical temporal envelope processing in ASD, revealing deficits in the ability of children with ASD to detect rapid changes in amplitude within broadband noise stimuli. These findings offer further support for particular impairments in detecting rapid (or brief) timing events within and between auditory stimuli among individuals with ASD. Impaired auditory gap detection, as found in the current study and reported by Bhatara et al. (2013), is also consistent with this notion. Discrepant findings for temporal processing of auditory stimuli of long versus short duration may reflect different neural mechanisms underlying timing for different durations (Buhusi & Meck, 2005).

This possibility could inform our understanding of the underlying neural circuitry that is affected in ASD.

Modality specificity of temporal processing deficits in ASD. Temporal processing abnormalities among individuals with ASD may be specific to the auditory domain, at least for shorter stimulus durations. Rapid temporal processing in the visual system, on the other hand, appears to be spared, or even enhanced in ASD. Research has shown intact visual temporal order judgment abilities in children with ASD (Kwakye et al., 2011), and enhanced visual simultaneity judgment thresholds in adolescents and adults with ASD (Falter et al., 2012). Enhanced temporal resolution and accumulation of information over short time intervals have been reported in the context of other visual tasks as well. Specifically, enhanced perception has been seen in studies examining visual inspection time (Scheuffgen, Happe, Anderson, & Frith, 2000; Wallace, Anderson, & Happe, 2009), delayed matching-to-sample for short duration static visual displays (Caron, Mottron, Berthiaume, & Dawson, 2006), and detection of visual motion direction for high-contrast gratings (Foss-Feig, Tadin, Schauder, & Cascio, in press). Contrasted with the literature on rapid auditory temporal processing, these findings suggest the possibility of a modality-specific dissociation in the integrity of rapid processing of sensory information in ASD, wherein impairments exist in the auditory modality alongside enhancements in the visual domain. While this dissociation is speculative at present, it would be useful for future research to examine its validity using unisensory temporal stimuli in both auditory and visual modalities, in the same sample of participants. In terms of its implications for neural mechanisms underlying the current findings, the proposed dissociation would suggest neural abnormalities localized within the auditory system or, at the very least, in structures that have lesser impact on visual system functioning.

Clinical relevance of findings. The present findings confirmed our hypotheses that impaired auditory gap detection in ASD would be associated with lower performance on several measures of language functioning. Specifically, we saw relations between increased gap detection thresholds and poorer performance on tasks of phonological processing and receptive language functioning. Thus, whereas one might wonder whether a 20% increase in gap detection threshold would have clinically significant effects, our correlational findings suggest that it does. Indeed, temporal resolution on the order of a few milliseconds is necessary for speech perception. For example, formant transitions during stop consonants (e.g., /ba/ and /da/) occur on the order of milliseconds, making very rapid temporal resolution of auditory information critical for accurate syllable discrimination (Tallal, Miller, & Fitch, 1993). In addition, impaired auditory gap detection abilities have been reported in individuals with dyslexia (e.g., Tallal, 1980) and Specific Language Impairment (e.g., Tallal & Piercy, 1973), which supports the role of rapid auditory temporal processing deficits in disorders characterized by primary language impairments. Interestingly, however, individuals with dyslexia and Specific Language Impairment have temporal processing deficits that span sensory modalities, affecting vision and touch, in addition to audition (Farmer & Klein, 1995; Tallal et al., 1993). If rapid temporal processing difficulties in ASD are indeed specific to the auditory modality, this feature may differentiate ASD from other disorders where both language and temporal processing are affected. This differentiation, in turn, may indicate that the neural mechanism of temporal processing deficits in ASD may lie within auditory system-specific circuitry, whereas the brain basis of temporal processing deficits in pure language and reading disorders may lie elsewhere.

The fact that we did not find relations between gap detection threshold and measures of sensory abnormalities or broader social communication deficits may indicate that rapid auditory

temporal processing deficits in ASD are most proximally related to language difficulties in this disorder. However, the presence of a relation between gap detection impairments and language difficulties even in a group of children with ASD with average or better IQ scores and strong verbal communication suggests that the nature of the relation between impaired temporal processing and language is likely complex. Nonetheless, rapid auditory temporal processing deficits, or at least increased gap detection thresholds, appear to be insufficient to explain broader deficits in ASD. Instead, they likely interact with other brain-based differences to produce the full ASD phenotype.

Strengths, limitations, and future directions. This study has a number of strengths, including a stringently-characterized clinical sample, a well-matched typically developing control group, a carefully controlled experimental procedure, and a reasonable sample size. These factors contribute to the confidence with which we can conclude that ASD is characterized by impaired ability to detect minute silent gaps in auditory stimuli. In addition, our finding that gap detection impairments relate strongly to language vulnerabilities supports the clinical importance of this low-level sensory processing deficit. One limitation of the study is that all participants were high functioning, with the mean IQ score in the High Average range. Thus, the presence (and extent) of a rapid temporal processing deficit in lower functioning individuals with ASD was not addressed. Along these lines, it stands to be clarified whether more severe rapid auditory temporal processing deficits among lower functioning individuals with ASD might in part explain their more substantial language impairments, or the absence of language altogether in some individuals.

The neural basis of impaired auditory gap detection abilities in ASD remains to be determined. Research in this area might help differentiate ASD from other disorders with

language-related deficits where more diffuse, multi-modal temporal processing impairments are reported. It also may offer important clues as to specific brain regions and cognitive processes that are impacted in ASD. To begin to address this question, it is important to consider whether deficits in rapid temporal processing are a result of failure to detect brief temporal changes in stimuli at a sensory level or, rather, whether breakdown might occur at a higher level, such as with perception and/or more conscious attention to rapid temporal input. To this end, we conducted an additional study in a subset of children who participated in Study I. The goal of the study that follows was to explore the brain response to near-threshold silent gaps in broadband noise. This study, reported in the next chapter, aimed to better understand the specific neural processes that underlie auditory gap detection deficits reported here.

CHAPTER III

Study II

Introduction

Understanding the neural processes associated with impaired auditory gap detection abilities in children with ASD may be helpful for several reasons. For example, it may shed light on the nature of the deficits, perhaps pointing to specific brain functions or regions that might underlie observed deficits in processing rapid temporal information in auditory stimuli. Further, it may suggest ways in which impaired detection of silent gaps in auditory stimuli fits with the broader clinical picture associated with ASD. Finally, it may indicate broader abnormalities in the timing or extent of the brain response to sensory stimuli that could help differentiate ASD from other disorders, and perhaps inform novel interventions.

Electrophysiological studies of auditory gap detection. A handful of studies have used electrophysiological methods to explore timing of the brain response to gaps in auditory stimuli, in both typical and hearing-impaired populations. Bertoli, Heimberg, Smurzynski, and Probst (2001) examined the mismatch negativity (MMN) response to silent gaps in pure tone stimuli, presented in background masking noise. In general, the MMN response indexes pre-attentive detection of deviance (in this case the presence of a gap) among repeated standard stimuli. Silent gaps of 9ms and 15ms duration consistently elicited MMN responses at frontal and central electrodes, but MMN was not elicited to gap sizes at or below behavioral detection thresholds determined in the same participants. However, MMN amplitude was larger and latency was earlier for longer gap durations, suggesting sensitivity of the event-related potential (ERP)

response to the relative detectability of gap stimuli. In elderly adults, differences in the MMN response to silent gaps have been reported even as differences in behavioral gap detection threshold were non-significant (Bertoli, Smurzynski, & Probst, 2002). Specifically, delayed latency and reduced amplitude of the MMN response were observed in older relative to younger participants, suggesting that the ERP response to silent gaps in auditory stimuli can reveal additional information regarding the nature of temporal processing deficits, above and beyond those detectable by behavioral procedures alone.

Michalewski, Starr, Nguyen, Kong, and Zeng (2005) examined the neural response associated with gap detection in a slightly different fashion. First, silent gaps were presented in continuous broadband noise, which contrasted with the pure tones used in the aforementioned studies. Second, instead of examining the MMN response to rare deviants containing silent gaps, Michalewski and colleagues assessed the N1 and P2 responses to gaps of various sub- and supra-threshold durations, during both active and passive listening conditions. N1 is an early negative-going peak that indexes selective attention to physical properties of sensory stimuli; P2 is a slightly later, positive-going peak that reflects feature detection and stimulus classification. N1 and P2 responses were elicited consistently for gap sizes 5ms or longer in duration, but were absent in response to a 2ms gap, which participants were unable to detect behaviorally. N1, and particularly P2, amplitudes were smaller for the 5ms gap condition, where behavioral detection rates were well below ceiling, relative to their amplitudes for longer gap conditions, where behavioral detection rates were almost 100%. This finding suggests that behavioral detectability is reflected in the magnitude of early ERP components in response to near-threshold stimuli. In the context of the present study, examining the dynamics of similar ERP components to near-threshold silent gaps in auditory stimuli among children with ASD and TD might help clarify the

reason shorter gaps can be detected by children with TD, whereas they remain undetected by children with ASD.

Study II Aims

The goal of Study II was to examine, using electrophysiological methods, the neural response to near-threshold silent intervals in noise during a gap detection task, in children with and without ASD. Thus, Study II sought to characterize early sensory components of the neural response to rapid timing events in auditory stimuli, and also to determine whether the underlying neural processes differed as a function of whether a near-threshold gap was consciously detected. The following hypotheses were tested:

Hypotheses

Hypothesis 1. Children with ASD and TD will differ in their neural responses to the onset of broadband noise. Specifically, following initial onset of the stimulus, the neural response of children with ASD will show prolonged N1 and P2 latency, relative to that of children with TD. This group difference is predicted since it would be consistent with findings from previous studies that have demonstrated delayed timing of the brain response to repeated auditory stimuli in ASD. The presence of such a delay might, in turn, affect the ability of children with ASD to resolve rapid temporal events that occur within a stimulus shortly after its onset.

Hypothesis 2. Children with ASD will show abnormalities in the neural response to near-threshold silent gaps in noise. This abnormality will be reflected in reduced N1 and P2 amplitude and delayed N1 and P2 latencies in response to the onset of the silent gap. Further, it is predicted

that group differences will be more salient for the subset of near-threshold stimuli for which participants responded that they could not detect the gap, despite its being present.

Method

Participants. Participants for this experiment were drawn from among those completing Study I. Thus, inclusion and exclusion criteria, and clinical characterization of the ASD group, were identical to those reported in Study I (see Chapter II; page 10 for details). An additional exclusion criterion was applied for Study II procedures: children who were taking psychotropic medications were excluded because we wanted to ensure group differences in medication status would not confound interpretation of ERP results. Among the 24 children with ASD who completed psychophysical thresholding procedures, four were excluded from participation in the procedures associated with Study II based on this criterion. An additional five completed the ERP tasks, but their data were excluded because of poor performance on the behavioral component of the ERP task (n=2), or excessive motion artifacts in the EEG signal (n=3). Among the 27 children with TD who completed the psychophysical procedures for Study I, three did not return to complete the ERP component of the study and are not included in Study II. ERP data from an additional seven were not included because of poor performance on the behavioral task (n=1) or poor EEG data resulting in too few remaining trials for analysis (n=6). Thus, ERP-related results are based on a subset of participants from the original sample, including 15 children with ASD and 17 children with TD.

ASD and TD groups in Study II remained matched on age, gender, handedness, and Full Scale IQ score (Table 3). Moreover, no significant differences in age or IQ score were seen in within-group comparisons of children with ASD and TD from Study I who did versus did not

have included data in Study II. Group differences in gap detection threshold not only remained significant in the Study II sample, but were, in fact, more pronounced. This difference appears largely driven by an increase in average threshold for the subset of participants with ASD included in Study II. When compared to the remaining participants with ASD from Study I not included here, Study II ASD participants had significantly higher ADOS Total Scores; therefore, our observation of higher gap detection thresholds in a sub-sample of participants with greater ASD symptoms is consistent with the assumption that more significant ASD symptomatology would be associated with larger deficits in auditory gap detection.

Table 3
Study II: Participant Demographics

Variable	**Group Means**		**Statistics**	
	ASD	**TD**	**Statistic**	***p*-value**
Age (years)	11.86 ± 1.4	12.23 ± 1.2	$t = 1.20$	0.24
Full Scale IQ	118.27 ± 13.8	112.56 ± 12.6	$t = -0.82$	0.42
Handedness[a]	12 R; 3 L	14 R; 1 L	$\chi^2 = 1.15$	0.30
Gender	14 M; 1 F	17 M; 0 F	$\chi^2 = 0.28$	0.47
Gap Detection Threshold	4.25 ± 1.5	3.11 ± 0.7	$\mathbf{t = 2.82}$	**0.008***

[a] Handedness information not available for 2 children with TD; * $p < 0.05$

Procedure. For details on study enrollment and procedures, see Study I. All participants with TD and participants with ASD who were not prescribed psychotropic medication were invited to return for an additional testing session in order to complete the electrophysiological task. For those who agreed, they were first shown the electrophysiology laboratory and introduced to the recording net at the end of their participation in the procedures associated with

Study 1. This was done in order to familiarize them with the novel procedure, and to increase their comfort on the day of their participation in Study II.

In order to complete the electrophysiological component of this study, participants were seated in front of a high refresh rate PC monitor, on which visual cues to guide task progression (e.g., when participants should respond, when breaks occurred) were presented. Auditory stimuli were presented via Etymotic Research ER-3A insert earphones to both ears. Volume of auditory stimuli was constant (80 dB) across participants. Both stimulus presentation and behavioral response recording were controlled by E-Prime (Psychology Software Tools Inc., Pittsburgh, PA, USA). Children initially watched television shows of their choosing on the computer screen while the experimenter placed the net and adjusted electrode impedances. Once the experiment began, lights were turned off to reduce line noise. Children were reminded to keep their eyes open and focused on the fixation cross on the computer screen, and to stay as still as possible. Participants were monitored via two closed-circuit video cameras and, when necessary, a researcher remained in the room to cue on-task behaviors or remind children to remain still. The experiment was completed in two runs, each lasting 12-15 minutes, with a break where children watched television, and an experimenter checked electrode impedances in between the two runs.

Measures. No additional clinical characterization measures were collected as part of Study II; cognitive, diagnostic, and demographic measures completed during Study I were used to confirm eligibility and to match groups for age, IQ, and handedness. The experimental task and procedures associated with recording electrophysiological brain response are described below.

Experimental task. For the ERP task, white noise stimuli containing silent gaps of various durations were presented individually on sequential trials, and participants' task was to

indicate whether or not each stimulus contained a gap. Each trial comprised presentation of a single auditory stimulus 1000ms in duration, during which time a white fixation cross remained on the computer screen. Gap onset occurred 400ms into the overall stimulus duration for all gap-size conditions. At the end of the auditory stimulus, the fixation cross turned red, indicating for participants to respond regarding whether they perceived a gap in the stimulus ("yes gap") or not ("no gap"). Each trial contained a 3000ms response window following auditory stimulus offset; this response window was terminated by the participant's button press response, thereby initiating onset of the next trial. Inter-trial intervals varied randomly between 800ms and 1500ms, during which time the white fixation cross remained on the screen.

Trial types included a no-gap condition, as well as five types of gap stimuli (i.e., 1ms[1], 3ms, 6ms, 10ms, 30ms gaps). As ERP procedures were conducted contemporaneously with psychophysics procedures, gap sizes were pre-selected during initial task design and could not be informed by either individual or group average thresholds from staircase procedures. Therefore, a range of gap sizes were included to be sure at least one condition captured the near-threshold point, at which participants would inconsistently detect the gap behaviorally. The near-threshold condition was of particular interest for determining whether the neural response to a gap in noise differs as a function of whether participants do or do not *perceive* the gap (i.e., despite the physical stimulus being identical). Overall, stimuli from the no-gap condition represented 28.6% of all trials, while the other gap sizes each comprised 14.3% of trials. The experiment was conducted in two runs of 280 trials each (approximately 12 minutes per run). Trial types were evenly distributed across the two runs and randomly interleaved throughout the experiment.

[1] ERP data from the 1ms gap condition were not included in analyses because behavioral detection of what should have been sub-threshold gap durations was much higher than expected by chance; thus, it is likely that the 1-ms gap stimulus inadvertently contained additional acoustic features that distinguished it from the no-gap condition.

Participants' task was to indicate whether they perceived a gap on each trial using a button press response on a hand-held Serial Response SRT box. Buttons corresponding to "yes gap" and "no gap" were counter-balanced across participants. All participants completed practice trials to confirm task comprehension prior to beginning recordings for the full task.

Data analysis.

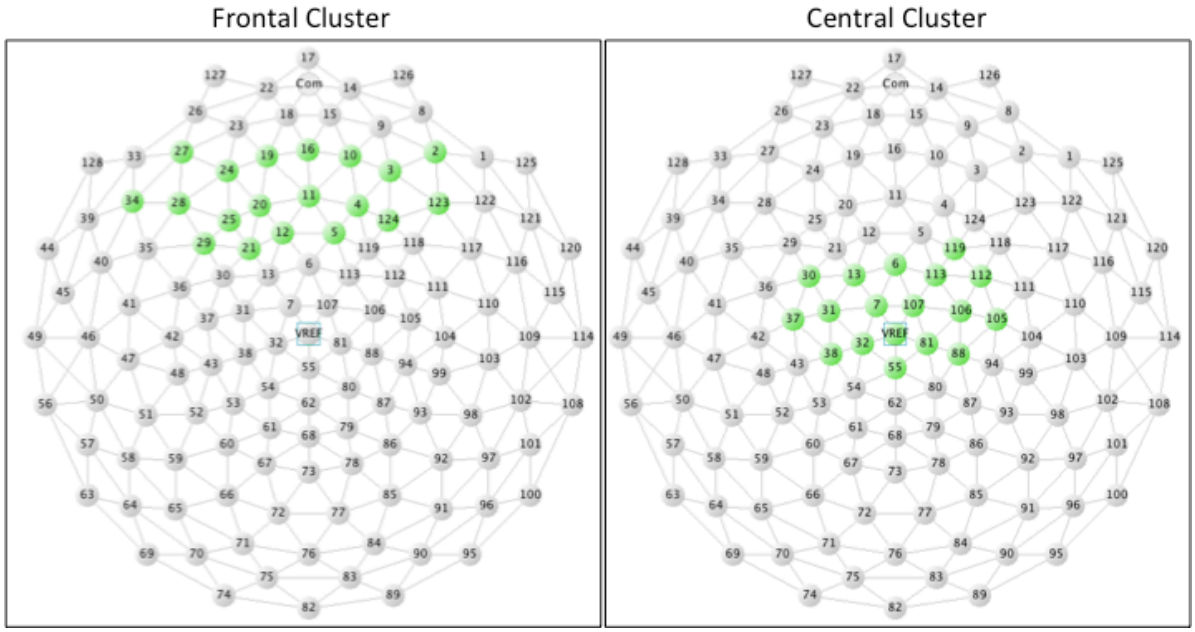
ERP acquisition and data pre-processing. EEG data were acquired in NetStation 4.3 (EGI, Inc., Eugene, OR, USA) using 128-channel high-density arrays (Geodesic Sensor Net, EGI, Inc., Eugene, OR, USA). Electrode impedances were kept below 40kOhms and checked before and after testing, as well as at breaks in task. Data were sampled at 1000Hz with filters set to 0.1-100Hz. All electrodes were referred to vertex during data collection, and then re-referenced to an average reference during post-processing. After data collection, a 60 Hz notch filter was applied to individual subject data files. Individual trials were then segmented into 1200ms epochs including 200ms pre-stimulus baseline and a 1000ms post-stimulus interval, beginning at the onset of the white noise stimulus. Trials were segregated by gap condition and performance accuracy. Single trial ERPs were screened for artifacts using automated procedures in NetStation. Trials contaminated by ocular or movement artifacts or with more than 15% "bad" electrode channels (i.e., those having poor signal quality) were rejected. For those trials having less than 15% bad electrodes, any electrodes identified as bad were replaced by reconstructing data using spherical spline interpolation procedures. Number of remaining trials per condition were comparable across groups ([reported as Mean ± SD] ASD: No Gap Correct: 56.40 ± 25.56; 3ms Detected: 14.47 ± 12.24; 3ms Undetected: 17.60 ± 12.92; 6ms Correct: 29.00 ± 14.37; 10ms Correct: 30.40 ± 13.72; 30ms Correct: 31.07 ± 12.65 TD: No Gap Correct: 66.87 ± 25.89; 3ms Detected: 15.80 ± 14.69; 3ms Undetected: 22.33 ± 11.14; 6ms Correct: 33.67 ± 14.09; 10ms

Correct: 34.93 ± 13.93; 30ms Correct: 34.60 ± 13.35). Following artifact removal, remaining data were averaged together across the two sessions per participant, re-referenced to an average reference (i.e., the mean across all 128 electrodes), and baseline corrected by subtracting the average microvolt value across the 200ms pre-stimulus period from the post-stimulus segment.

ERP data analysis. To reduce the number of electrodes in the analysis, data from 128 electrodes were submitted to a spatial principal components analysis (sPCA; Spencer, Dien, & Donchin, 1999). This analysis was conducted in order to determine a small set of "virtual electrodes," each representing a spatially contiguous cluster of electrodes that yielded similar ERP waveforms. Specific electrodes comprising each cluster were identified as having factor loadings of |.6| or greater, with those electrodes meeting criteria for inclusion in multiple clusters being placed in the cluster where the factor loading score was greater. Data for electrodes within each resulting cluster were averaged for analyses. For the purpose of analyses, frontal and central clusters emerging from sPCA procedures were selected in order to examine ERP responses to auditory events. Electrodes comprising the two clusters are shown in Figure 2.

Next, mean amplitude and latency measures were computed for frontal and central P1 (30-70 ms), N1 (70-130ms), and P2 (150-200ms) components using an automated scoring tool in NetStation 4.4. Time windows were selected based on a combination of intervals used in previously published studies of auditory gap detection (Bertoli et al., 2002; Michalewski et al., 2005) and on visual inspection of the grand average waveforms from the present dataset. ERP components were scored for response to initial stimulus onset and, separately, for response to gap onset, with "0ms" coinciding with 400ms into the post-stimulus interval. See Figure 3 for illustration of analysis windows.

Figure 2

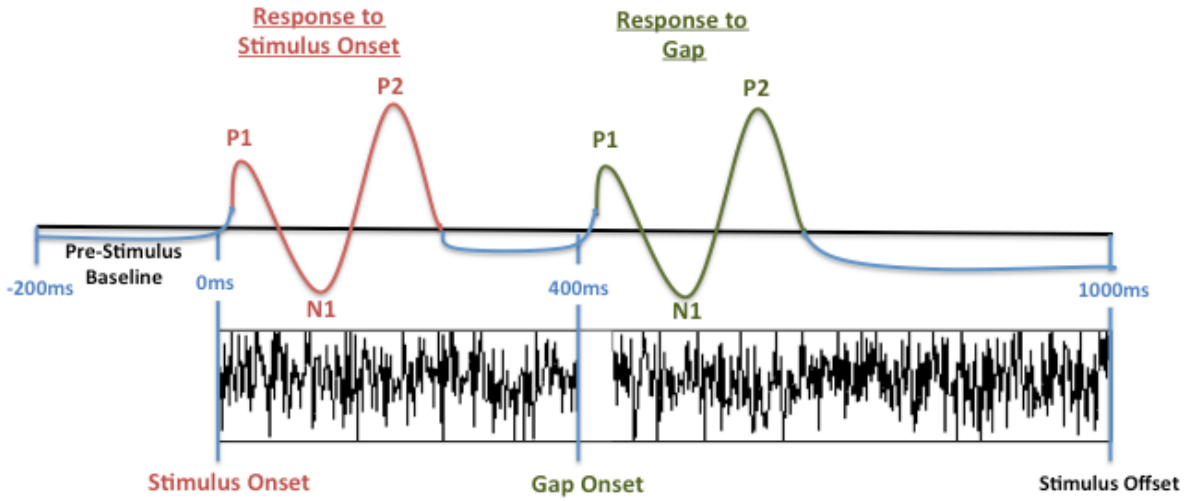


Frontal and Central Electrode Clusters Emerging from sPCA Analyses.

Mean (as opposed to peak) amplitude was chosen for measurement because it is less sensitive to noise, is unaffected if maximum peak amplitude falls outside the selected window for some participants and/or electrodes, and is a linear measure (and thus provides measurement values that are consistent with the grand average waveform) (Luck, 2005).

Mean P1, N1, and P2 amplitude and latency measures in response to stimulus onset were averaged across gap conditions, as all stimuli were identical in the initial portion. Repeated measures ANOVAs were then conducted separately for each component (P1, N1, and P2) and index (amplitude and latency) with Cluster (Frontal, Central) as the within-subjects effect and Group (ASD, TD) as the between-subjects effect. Follow-up analyses with independent-samples *t*-tests were also conducted in order to clarify group differences.

Figure 3



Schematic of Analysis Windows for Response to both Stimulus and Gap Onset in a Single Trial.

To examine neural response to behaviorally detected and undetected gaps of near-threshold durations, P1, N1, and P2 mean amplitude and latency were computed for each individual. Specifically, components were scored separately for 3ms Gap trials when they were "Detected" (participant indicated he/she heard a gap) versus when they were "Undetected" (participant indicated he/she did not hear a gap). The 3ms gap condition was selected because it was the only condition with sufficient number of behavioral responses indicating both detected and undetected gaps, and because the gap duration was nearest to the gap detection threshold identified in Study I. Six separate 2x2x2 repeated measures ANOVAs were conducted. For each component (P1, N1, and P2), ANOVAs were conducted for both amplitude and latency, with Cluster (Frontal, Central) and Gap Detection Accuracy (Detected, Undetected) as the within-subjects effects and Group (ASD, TD) as the between-subjects effect. Additional analyses using ANOVAs and *t*-tests were employed to clarify the specific scalp sites, task conditions, and neural markers that best differentiated children with ASD from those with TD.

Results

Behavioral results. Accuracy and reaction time were compared between groups for each condition. Mean reaction times were computed for each condition using only trials where participants responded correctly as to whether or not a silent gap was present in the stimulus. Results are presented in the table below (Table 4).

Table 4
Behavioral Results from electrophysiological study of auditory gap detection.

Condition	Accuracy (% Correct)		Mean Reaction Time (ms)		d'	
	ASD	**TD**	**ASD**	**TD**	**ASD**	**TD**
No Gap	**82.04 ± 10.2***	**88.94 ± 7.6***	535.11 ± 152.4	502.46 ± 167.0	--	--
3ms Gap	45.57 ± 26.3	36.69 ± 26.9	569.48 ± 209.5	666.95 ± 231.3	-0.21 ± 1.2	0.19 ± 1.0
6ms Gap	95.31 ± 5.0	94.95 ± 4.9	459.75 ± 156.7	456.89 ± 131.3	-0.35 ± 1.6	-0.31 ± 1.3
10ms Gap	96.05 ± 4.3	95.93 ± 4.3	455.24 ± 152.8	444.55 ± 141.8	-0.37 ± 1.6	0.33 ± 1.3
30ms Gap	96.04 ± 4.1	96.19 ± 4.2	450.61 ± 145.7	455.97 ± 142.1	-0.41 ± 1.6	0.36 ± 1.4

* $p < 0.05$

Children with ASD were significantly less accurate for the No Gap condition, $t(30) = -2.185$; $p = 0.037$, Cohen's $d = 0.774$, but no group differences in response accuracy were observed at any other condition (all ps > 0.35). For both groups, accuracy rates were close to ceiling (i.e., 95% or better) for gap sizes of 6ms or greater. Signal detection analyses were conducted for each gap condition. For these analyses, Hit rate was computed separately for each condition as the proportion of trials on which participants correctly detected the gap (e.g., 3ms Gap Detected/(3ms Gap Detected + 3ms Gap Undetected)). False Alarms were always defined as

the proportion of trials in the No Gap condition for which participants incorrectly responded that a gap was present (i.e., No Gap Error/(No Gap Correct + No Gap Error)). Z-scores were computed for Hit and False Alarm rates and d-prime was calculated. Independent-samples *t*-tests revealed no group differences in response bias for any of the gap conditions (all *p*s > 0.15).

No group differences in reaction time were observed for any condition on trials where participants responded correctly as to the presence or absence of a gap (all *p*s > 0.22).

ERP response to stimulus onset. Repeated measures ANOVAs examining effects of Cluster and Group on the latency of neural response to the initial onset of a white noise stimulus were conducted separately for each component (P1, N1, and P2). For two of three ANOVAs (i.e., P1 and N1 latency), there were significant main effects of Cluster (P1: $F(1, 1) = 27.67$, $p < 0.001$; N1: $F(1, 1) = 16.24$, $p < 0.001$) that were not of interest for study questions, particularly given that there were no significant cluster by group interactions (all $p > 0.23$). Thus, between-group comparisons were conducted separately for frontal and central clusters using independent samples *t*-tests (Table 5).

It was hypothesized that we would observe longer latencies of early sensory components in ASD relative to TD. However, results did not support this hypothesis. No group differences were seen in the latency of either the N1 or P2 responses at frontal or central clusters. Results did reveal a difference between groups in the latency of frontal P1 response to stimulus onset; however, the direction of this difference was opposite than that hypothesized. On average, P1 latency was significantly shorter in children with ASD than in children with TD, $t(30) = -2.36$, $p = 0.025$, Cohen's $d = 0.836$. The ERP response to stimulus onset at the frontal cluster is visualized in Figure 4.

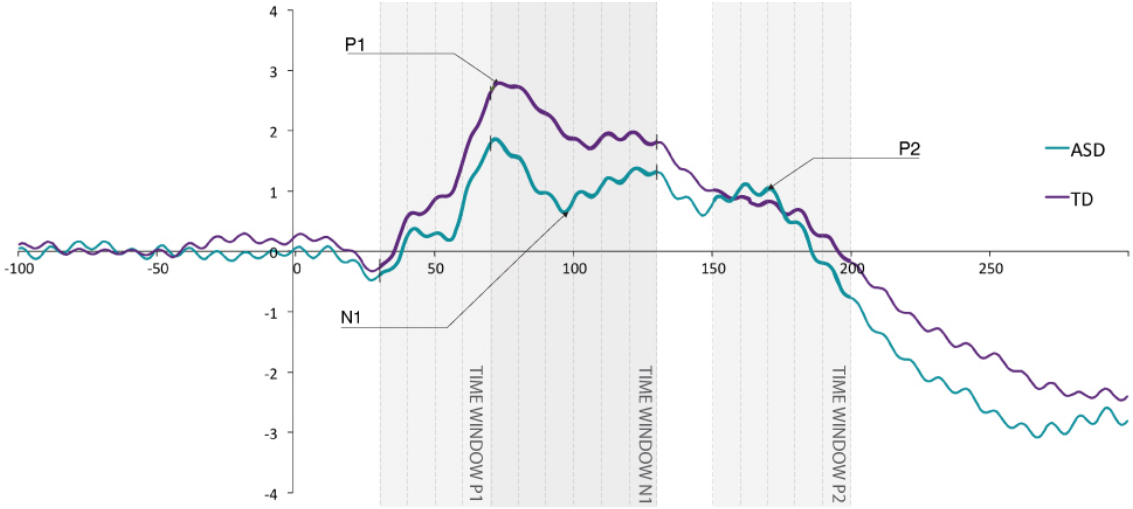
Table 5

Mean Latencies and Amplitudes in Response to Initial Stimulus Onset.

Cluster	Component	Group Means		Statistics		
		ASD	TD	*t*-statistic	*p*-value	Cohen's *d*
		Latency (ms)				
Frontal	**P1**	60.05 ± 4.92	63.64 ± 3.67	-2.36	**0.025***	**0.836**
	N1	101.93 ± 10.97	106.78 ± 8.46	-1.41	0.169	0.499
	P2	167.39 ± 7.31	169.95 ± 5.93	-1.10	0.282	0.390
Central	**P1**	55.86 ± 6.47	56.92 ± 5.18	-0.51	0.611	0.181
	N1	96.57 ± 8.04	97.33 ± 7.54	-0.28	0.782	0.099
	P2	167.08 ±7.22	168.84 ± 8.19	-0.64	0.527	0.227
		Amplitude (μV)				
Frontal	**P1**	0.46 ± 0.62	0.98 ± 0.87	-1.92	**0.064⁺**	0.680
	N1	1.18 ± 0.96	2.12 ± 1.31	-2.28	**0.030***	0.808
	P2	0.42 ± 1.91	0.57 ± 1.55	-0.24	0.811	0.085
Central	**P1**	0.44 ± 0.73	0.56 ± 0.87	-0.42	0.678	0.149
	N1	0.70 ± 1.01	1.17 ± 1.37	-1.09	0.285	0.386
	P2	2.34 ± 1.78	2.44 ± 1.76	-0.16	0.875	0.057

* $p < 0.05$; $^{+}$ $p < 0.10$

Figure 4



ERP Response to Initial Stimulus Onset at the Frontal Cluster.

As a part of an exploratory analysis driven by visual observations comparing the grand averaged waveforms between groups, we examined group differences in the amplitudes of the P1, N1, and P2 responses. As for latency analyses, separate repeated measures ANOVAs were conducted for P1, N1, and P2 mean amplitude. As for latency results, there were significant main effects of Cluster for two of three ERP components (N1: $F(1, 1) = 14.41$, $p = 0.001$; P2: $F(1, 1) = 59.68$, $p < 0.001$) that were not relevant given study questions and hypotheses, particularly given that no group by cluster interactions were revealed (all $p > 0.22$). Thus, follow-up *t*-tests were again conducted to explore group differences at individual scalp locations. In these analyses, differences were revealed in the mean amplitude of the P1 and N1 responses at the frontal cluster (see Table 4). Specifically, a trend was seen for larger P1 mean amplitude in TD relative to ASD children. N1 mean amplitude, on the other hand, was greater in ASD relative to TD children.

Comparison of peak-to-peak mean amplitudes for P1-N1 revealed no significant group differences, $t(30) = -1.07$, $p = 0.29$, Cohen's $d = 0.379$. In other words, the negative deflection occurring after the P1 peak was equivalent in magnitude across ASD and TD groups, though the mean amplitude in the N1 window suggested a more negative mean amplitude in the ASD group. This peak-to-peak finding suggests that the apparent group differences in the amplitude of the N1 response may be due to a more global shift in the ERPs, with TD participants having more positive amplitudes in the analyzed window, as a result of their larger P1 response in the preceding time interval. Thus, as related to the amplitude of ERP component responses to onset of a white noise stimulus, the primary between-group difference is decreased P1 amplitude over frontal electrodes in the ASD group. No group differences in amplitude of the P2 response were revealed.

ERP response to near-threshold gaps. Analyses were next conducted to evaluate group differences in the ERP response to near-threshold gaps in auditory stimuli, particularly as a function of whether participants could detect the gap behaviorally. Omnibus ANOVAs for P1 amplitude and latency, N1 amplitude, and P2 latency all yielded no significant main effects or interactions (all p-values = 0.13 – 0.89) The omnibus repeated-measures ANOVA for N1 latency revealed a trend for a main effect of cluster and a statistically significant accuracy by group interaction. In addition, the omnibus ANOVA for P2 amplitude revealed trends ($p < 0.10$) for a main effect of group, and for cluster by group, cluster by accuracy, and cluster by group by accuracy interactions. Results of the omnibus ANOVAs for N1 latency and P2 amplitude are reported in Table 6.

Table 6

Main Effects and Interactions for Analyses of Mean Amplitude and Latency in Response to Gap Onset.

Latency

Peak	Factor	Mean Square	*F*-statistic	*p*-value
N1	Cluster	565.07	3.210	**0.083⁺**
	Group	307.67	1.384	0.249
	Accuracy	181.04	0.792	0.381
	Cluster x Group	196.83	1.118	0.299
	Accuracy x Group	1567.49	6.856	**0.014***
	Cluster x Accuracy	6.01	0.041	0.841
	Cluster x Accuracy x Group	146.75	0.998	0.326

Amplitude

	Factor	Mean Square	*F*-statistic	*p*-value
P2	Cluster	16.35	1.337	0.257
	Group	89.61	3.200	**0.084⁺**
	Accuracy	1.165	0.092	0.764
	Cluster x Group	38.63	3.159	**0.086⁺**
	Accuracy x Group	0.62	0.049	0.826
	Cluster x Accuracy	36.53	3.819	**0.060⁺**
	Cluster x Accuracy x Group	28.20	2.948	**0.096⁺**

* $p < 0.05$; $^{+}$ $p < 0.10$

Follow-up *t*-tests were conducted to better understand group differences in N1 latency and P2 amplitude suggested by the omnibus ANOVA. Group comparisons were conducted separately for detected and undetected gaps, at frontal and central clusters (Table 7).

Table 7

Mean Latencies and Amplitudes in Response to Gap Onset.

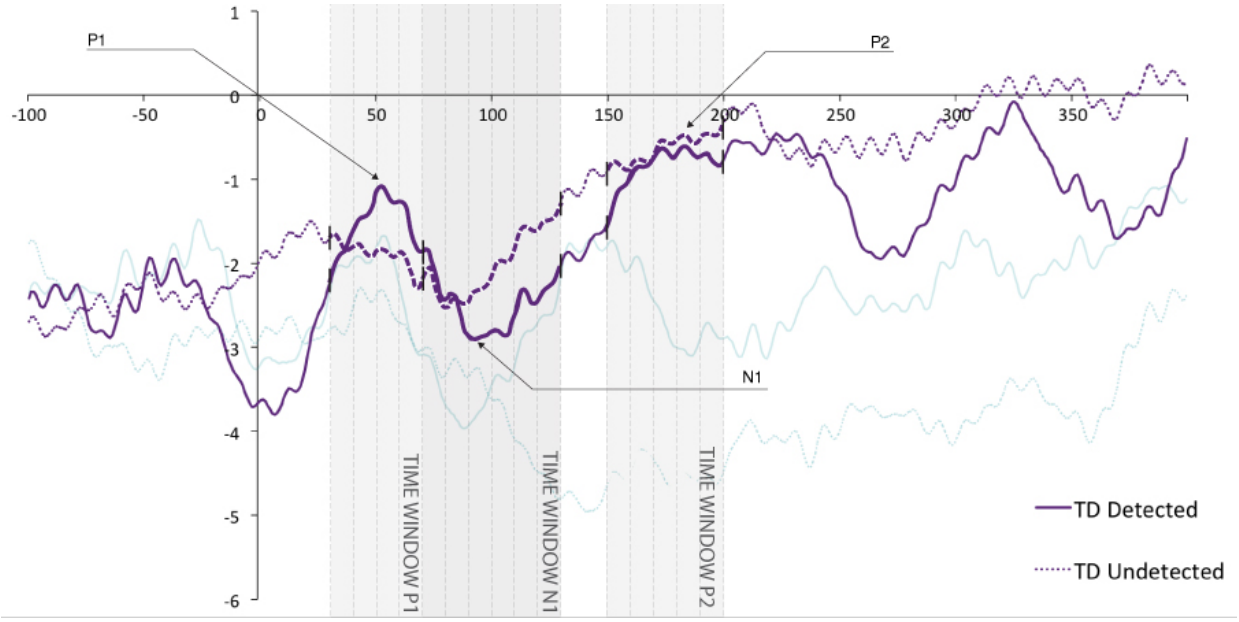
Cluster	Peak	Accuracy	Group Means		Statistics^		
			ASD	TD	*t*-statistic	*p*-value	Cohen's *d*
Latency (ms)							
Frontal	**P1**	Detected	450.55 ± 8.87	452.62 ± 10.24	--	--	--
		Undetected	450.34 ± 9.77	449.95 ± 11.50	--	--	--
	N1	Detected	501.73 ± 17.21	505.98 ± 15.89	-0.725	0.474	-0.257
		Undetected	509.42 ± 12.35	503.93 ± 12.47	1.248	0.222	0.442
	P2	Detected	576.80 ± 14.37	573.48 ± 9.96	--	--	--
		Undetected	577.85 ± 14.75	582.82 ± 9.48	--	--	--
Central	**P1**	Detected	450.23 ± 7.16	451.82 ± 8.58	--	--	--
		Undetected	448.45 ± 9.86	446.23 ± 9.21	--	--	--
	N1	Detected	498.30 ± 12.79	501.86 ± 16.37	-0.680	0.502	-0.244
		Undetected	509.40 ± 13.09	494.65 ± 9.47	3.683	**0.001***	1.308
	P2	Detected	575.11 ± 15.55	577.10 ± 8.14	--	--	--
		Undetected	576.59 ± 11.29	577.87 ± 9.88	--	--	--
Amplitude (μV)							
Frontal	**P1**	Detected	-3.32 ± 4.64	-2.52 ± 4.50	--	--	--
		Undetected	-1.62 ± 3.45	-3.06 ± 1.92	--	--	--
	N1	Detected	-4.21 ± 5.29	-2.95 ± 4.10	--	--	--
		Undetected	-2.75 ± 3.69	-3.52 ± 2.64	--	--	--
	P2	Detected	-4.16 ± 5.08	-2.78 ± 4.84	-0.784	0.439	0.278
		Undetected	-2.10 ± 3.96	-2.32 ± 2.83	0.187	0.853	0.065
Central	**P1**	Detected	-2.19 ± 1.77	-1.53 ± 4.02	--	--	--
		Undetected	-2.64 ± 3.48	-1.89 ± 1.87	--	--	--
	N1	Detected	-3.26 ± 2.06	-2.49 ± 3.22	--	--	--
		Undetected	-3.76 ± 4.35	-2.00 ± 1.61	--	--	--
	P2	Detected	-2.53 ± 2.58	-0.84 ± 3.88	-1.437	0.161	-0.523
		Undetected	-4.49 ± 4.92	-0.63 ± 2.72	-2.790	**0.009***	-1.010

* $p < 0.05$; $^{+}$ $p < 0.10$

^Group means for amplitude and latency measures for all peaks, conditions, and scalp locations are reported; however, statistics were only computed for indices where the omnibus ANOVA indicated at least one significant main effect or interaction. Dashed lines indicate where statistical tests were not applied.

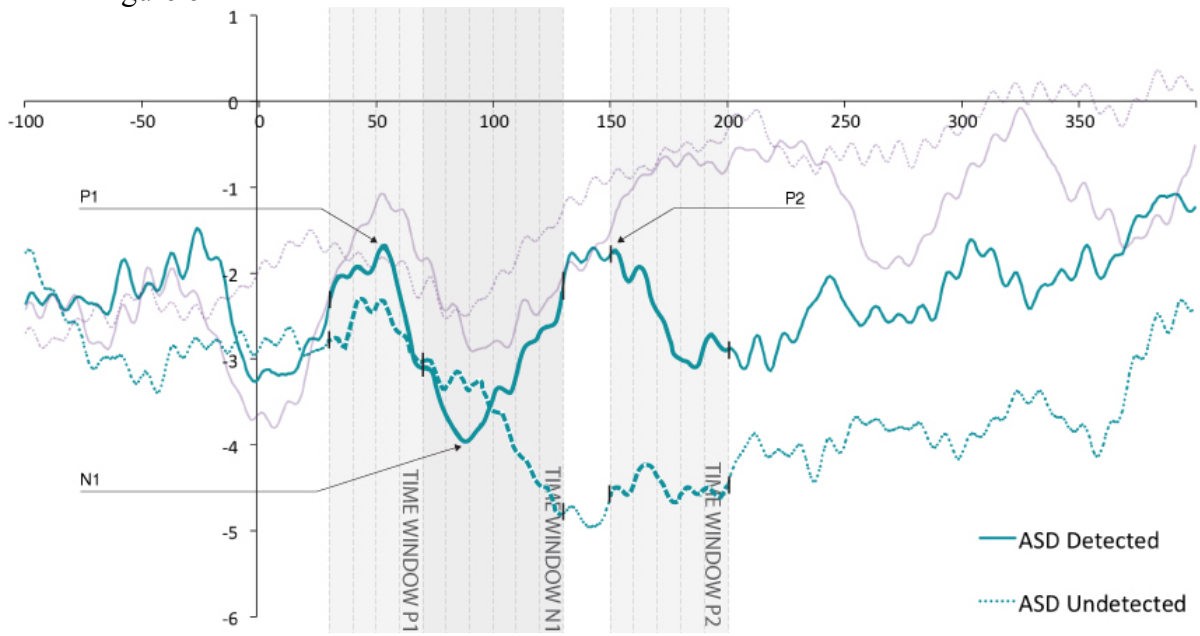
No group differences in N1 latency or P2 mean amplitude were detected at either frontal or central clusters for the subset of trials within the 3ms gap condition where participants accurately detected the presence of the silent gap. Group differences were, however, observed in the neural response to behaviorally undetected 3ms gaps. Specifically, significant group differences in N1 latency and in P2 amplitude were both observed at the central (but not frontal) cluster. As predicted by our initial hypothesis, children with ASD had a longer N1 latency when near-threshold gaps were behaviorally undetected. Children with ASD had a substantially smaller P2 mean amplitude in this condition as well. ERP responses to behaviorally detected and undetected 3ms gaps are highlighted in Figure 5 for the TD group and Figure 6 for the ASD group, with waveforms for the alternate group visible in the background for visualization of between-group differences.

Figure 5



ERP Response to Gap Onset in Children with TD.

Figure 6



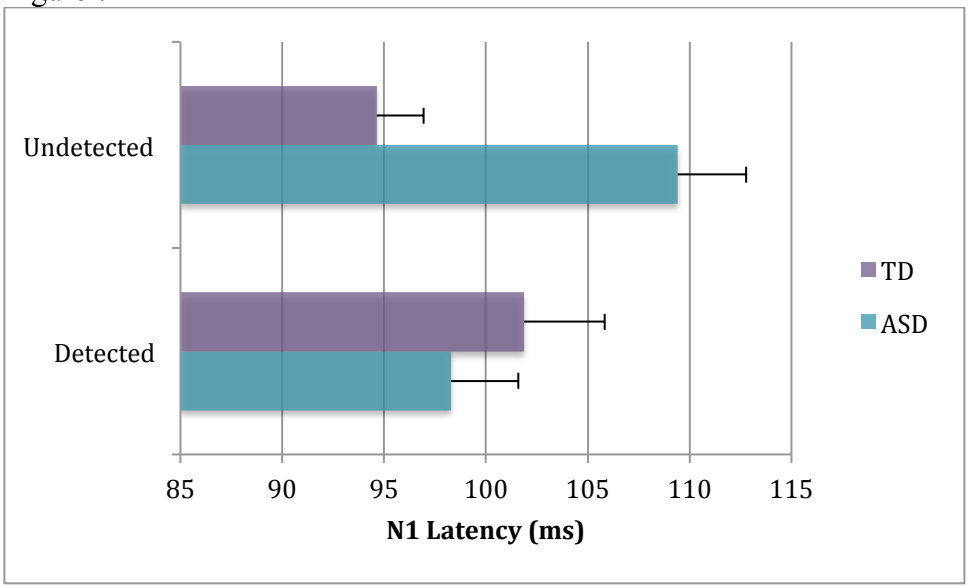
ERP Response to Gap Onset in Children with ASD.

Visual inspection of the waveforms for behaviorally detected and undetected gaps in ASD appeared to suggest substantial differences in the ERP response dependent on behavioral detection. The fact that N1 latency and P2 amplitude differences at the central cluster were significantly different between participants with ASD and TD for behaviorally undetected (but not for detected) 3ms gaps provides some evidence supporting this observation. However, we conducted an additional set of exploratory repeated measures ANOVAs for N1 latency and P2 amplitude at the central cluster in order to simplify the three-way interaction tested above. Furthermore, this additional analysis aimed to enable us to quantify differences by group and detection accuracy that were visibly apparent in plotted waveforms (Figures 4 and 5). In other words, these additional exploratory analyses were conducted in order to determine whether the neural response to the 3ms gap was differentially associated with behavioral detection across

ASD and TD groups. Hence, the within-subjects factor was Gap Detection Accuracy (Detected, Undetected) and the between-subjects factor was Group (ASD, TD).

For N1 latency, no main effect of accuracy was observed, $F(1,1) = 0.357$, $p = 0.56$. Though the main effect of group was not statistically significant, $F(1,1) = 2.81$, $p = 0.10$, there was a weak trend for increased N1 latency in the ASD group overall. Results revealed a statistically significant group by accuracy interaction, $F(1,1) = 7.874$, $p = 0.009$. This interaction appears to reflect an increase in N1 latency in the ASD group when gaps were undetected behaviorally, whereas N1 latency shortened in the TD group when gaps were behaviorally undetected (Figure 7).

Figure 7



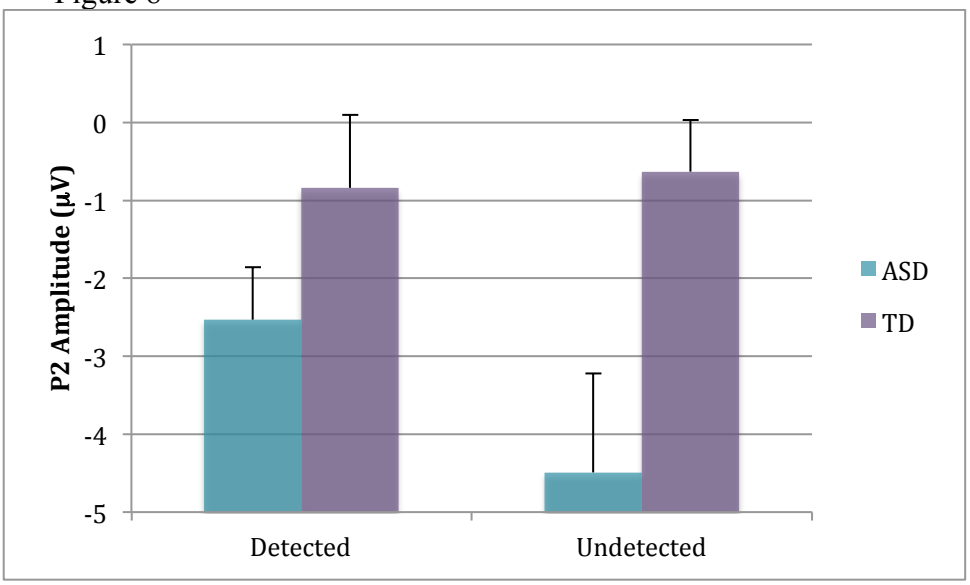
Mean Post-Gap N1 Latency to Detected versus Undetected Gaps.

For the ASD group, paired *t*-tests indicated that the difference in N1 latency for detected versus undetected gaps was statistically significant, $t(15) = -2.387$, $p = 0.032$, Cohen's $d = 0.616$.

In general, N1 latency was longer in the ASD group than the TD group for 3ms gaps, whether or not gaps were detected behaviorally.

For P2 amplitude, no main effect of accuracy was observed, $F(1,1) = 1.197$, $p = 0.28$. However, a significant main effect of group was revealed, $F(1,1) = 7.656$, $p = 0.01$, wherein P2 amplitude to 3ms gaps was smaller in ASD than in TD, regardless of whether the gap was behaviorally detected (Figure 6). While there was no significant group by accuracy interaction, $F(1,1) = 1.806$, $p = 0.19$, plots suggest that the amplitude of the P2 response to near-threshold silent gaps was independent of behavioral detection in the TD group, whereas there was a notable absence of a P2 response in children with ASD when they failed to detect the gap behaviorally (Figure 8).

Figure 8



Mean Post-Gap P2 Amplitude to Detected Versus Undetected Gaps.

For the ASD group, paired *t*-tests indicated that the difference in P2 amplitude for detected vs. undetected gaps was not statistically significant, $t(15) = 1.522$, $p = 0.15$, Cohen's $d = 0.423$; however, the effect size was moderate.

Discussion

This study sought to evaluate the neural response to near-threshold gaps in auditory stimuli in children with ASD and TD. In particular, it focused on differences in the ERP response to near-threshold gaps as a function of whether they were or were not detected behaviorally. ERP analyses indicated group differences in response to the onset of a white noise stimulus in ASD. In addition, group differences were revealed in the ERP response to behaviorally undetected silent gaps of near-threshold duration. Behavioral results did not reveal differences between groups in accuracy or response time to silent gaps in white noise stimuli, independent of the duration of the gap. Children in both groups performed near chance with regard to their ability to behaviorally detect silent gaps 3ms in duration, which is consistent with the auditory gap detection threshold values reported in Study I. Children in the ASD group were slightly but significantly less accurate in their response to stimuli without a gap; however, *d*-prime values did not differ by group, indicating that the slightly higher rates of false alarms (i.e., reported gaps on No Gap trials) in ASD did not affect overall signal detection.

ERP response to stimulus onset. In response to white noise onset, we did not find expected delays in N1 or P2 latency among children with ASD. In fact, no differences in the N1 or P2 response were revealed at all. Instead, over frontal electrodes, children with ASD showed faster *P1* latency, but reduced P1 amplitude, relative to children with TD. Results from a magnetoencephalography (MEG) study of response to pure tone stimuli are consistent with our

findings of typical N1 response to sound onset (Oram Cardy, Ferrari, Flagg, Roberts, & Roberts, 2004). Specifically, Oram Cardy and colleagues found comparable M100 (i.e., the MEG counterpart to the N1 ERP response) responses between children with and without ASD, which supports our finding of intact N1 response to sound onset. However, their results related to the P1 component differ from ours. Specifically, whereas Oram Cardy and colleagues reported typical M50 (i.e., MEG equivalent of P1) responses in ASD, P1 responses in our study were characterized by earlier latency and smaller amplitude in ASD relative to TD. It is possible that discrepancies in the integrity of this early sensory response are a function of stimulus differences between our study and that of Oram Cardy and colleagues (e.g., that we used more complex auditory stimuli). If this is the case, abnormalities in early sensory processing among children with ASD may be specific to complex stimuli, such as the broadband noises used in this study.

Our finding of earlier P1 latency and reduced P1 amplitude in ASD may relate to differences in preferential attention to sensory events, as the auditory P1 (also termed P50) response is thought to reflect increased arousal triggered by the incoming sensory stimuli (Key, Dove, & Maguire, 2005). Consistent with this functional understanding of the auditory P1 response, it has been proposed that the auditory P1 is associated with neural activity in the reticular activating system (RAS), which regulates arousal (Buchwald et al., 1991). Thus, our P1 latency finding suggests that children with ASD are quicker to attend to onset of auditory stimuli, which is consistent with the notion of hyper-sensitivity to auditory input among individuals with ASD. However, the magnitude of the P1 response to auditory stimulus onset was smaller in this study, suggesting less coordinated activity of responding neurons in producing a cohesive, unified response. Hypo-responsiveness to sensory stimuli that is seen behaviorally in ASD could be consistent with the reduced P1 amplitude seen here. Specifically, while at some level children

with ASD may be hyper-sensitive and overly quick to divert attention to the onset of sensory stimuli, they do not in the end allocate as much coordinated attention to process the stimulus, perhaps then resulting in behavioral hypo-reactivity and failure to orient to sound. Thus, the present ERP findings could explain patterns of both hyper- and hypo-responsiveness to auditory input that are commonly concurrently seen among individuals with ASD.

ERP response to silent gaps in noise. Neural response to near-threshold silent gaps in white noise stimuli was evaluated separately dependent on whether gaps were or were not behaviorally detected. Analyses were limited to the 3ms gap condition, as that gap duration most closely corresponded to gap detection thresholds revealed in Study I, and because only this condition resulted in a sufficient number of trials for both behaviorally-detected and behaviorally-undetected gaps. Overall, children with ASD had increased N1 latency and decreased P2 amplitude in response to silent gaps 3ms in duration. However, both findings were largely driven by group differences when gaps were behaviorally undetected.

For individuals with ASD, the latency of the N1 response was significantly delayed on trials where they did not behaviorally detect the silent gap, relative to trials where they did detect the gap. Further, on trials where gaps were not detected, N1 latency was significantly delayed in the ASD relative to the TD group. N1 response is associated with detection of and selective attention to sensory and physical properties of an auditory stimulus, including its timing; thus, delayed N1 response to 3ms silent gaps in the undetected condition for children with ASD could indicate difficulty resolving whether the gap was indeed present (and thus in need of being attended to). The lack of differences in N1 amplitude – either between groups or between accuracy conditions – suggests that equivalent attention initially was directed to 3ms gaps across

groups, whether or not gaps were processed to the extent that they would ultimately result in conscious awareness of their presence.

On the subset of 3ms gap trials where children with ASD did not behaviorally detect the presence of a gap, they showed markedly reduced P2 amplitude, both relative to their own neural response to behaviorally-detected 3ms gaps, and relative to the neural response of children with TD to behaviorally-undetected gaps. This result suggests that children with ASD are less sensitive to near-threshold silent gaps in auditory stimuli. The P2 component is thought to be associated with attention modulation and stimulus classification (Key et al., 2005). Whereas the earlier N1 response reflects more basic sensory registration of a stimulus, the P2 response may reflect perceptual processing closer to conscious registration and attention. Thus, the combination of delayed N1 response and diminished P2 response to behaviorally-undetected near-threshold gaps suggests that when the physical presence of the gap becomes more difficult to detect at a primary level, subsequent perceptual processes may fail to engage for children with ASD. In other words, in some instances 3ms gaps that initially attracted some attention in the brains of children with ASD may not subsequently be accurately classified as containing gaps. The behavioral manifestation of this atypical neural response might be that individuals with ASD are ultimately hypo-responsive to near-threshold temporal changes in auditory stimuli. Particularly given that the ability to detect (and more completely process) temporal aspects of auditory stimuli on the order of few milliseconds is necessary for accurate speech perception, and that individuals with ASD have higher gap detection thresholds, the results seen for behaviorally-undetected gaps may have particular clinical significance.

Comparisons with other studies of ERP response to auditory gap detection. Our results suggest that delayed N1 in ASD reflects slower processing of near-threshold gaps, which

in some instances leads to failure to direct attention to the gap and, as a result, failure to consciously register its presence in order to behaviorally report its detection. There is some evidence that delayed N1 response during gap detection could be a marker of broader auditory processing, and perhaps also language, impairment. In their study of detection of near-threshold gaps in broadband noise, Michalewski and colleagues (2005) reported delayed N1 responses in adults with auditory neuropathy, who have both impaired auditory temporal processing and poor speech recognition. Bertoli et al. (2002) noted that healthy elderly adults, who have difficulty with speech perception, had delayed MMN latency to silent gaps. Some have theorized that the MMN response is simply a modulated expression of the auditory N1 (May & Tiitinen, 2010). Thus, both findings support the notion that the N1 latency delay observed in the current study could be a marker of clinically-relevant auditory processing impairments in ASD, given that it is also seen in other populations with known auditory and language processing deficits.

Our P2 results suggest that, for near-threshold gaps to be registered behaviorally in ASD, they must result in engagement of processes associated with attention modulation and stimulus classification. Where engagement of these processes fails to occur (and a P2 response fails to be generated), children with ASD do not become consciously aware of, and are unable to report detection of, silent gaps in noise. Michalewski and colleagues (2005) reported absent N1 and P2 responses to sub-threshold (i.e., 2ms) gaps among healthy adults, with both components emerging in response to a 5ms gap, but still having smaller amplitude to 5ms gap size relative to the amplitudes seen for longer gap durations. This observation was particularly true for the P2 response in the Michalewski et al. study, which is consistent with our finding that the P2 response appears particularly sensitive to detectability of near-threshold gaps. Michalewski and colleagues did not examine neural response to 5ms gaps separately based on whether gaps were

detected behaviorally. However, their findings of reduced P2 (and N1) amplitude, in conjunction with less consistent behavioral detection rates for 5ms gaps, suggest some congruence with our findings regarding differential neural responses to behaviorally detected and undetected near-threshold gaps. Why effects of P2 amplitude on behavioral detection of gaps was specific to the ASD group in the current study remains to be explored in future research.

Comparison to studies of brain response to auditory timing information in ASD. Our findings of delayed N1 and diminished P2 responses to rapid temporal changes in auditory stimuli support the notion of atypical neural response to timing information within auditory stimuli among individuals with ASD. Three previous studies have reported findings consistent with those seen here. First, Lepisto and colleagues reported reduced amplitude of the MMN response to duration deviants in both children with autism (Lepisto et al., 2005) and with Asperger's Disorder (Lepisto et al., 2006). As previously mentioned, there is some evidence that the MMN is essentially an amplitude- and latency-modulated N1 response (May & Tiitinen, 2010). Thus, the findings of Lepisto et al. support our results regarding early sensory ERP components being reduced in ASD in response to temporal information in auditory stimuli.

Interestingly, our P2 findings may offer some insight into the functional significance of MMN reductions seen in the Lepisto et al. studies. Specifically, because the task used by Lepisto and colleagues did not require that participants indicate behaviorally whether or not they detected deviance in stimulus duration for each trial, it is impossible to know whether MMN reductions reflected failure to behaviorally (or consciously) detect duration deviants, or whether these reductions would be seen regardless of behavioral detection. The specificity of P2 amplitude decreases in ASD for behaviorally-undetected gaps observed in the current study alludes to the possibility that duration deviants in the Lepisto et al. studies might not have

reached conscious awareness for detection if the experimenters had requested it. The fact that children with ASD in the Lepisto et al. studies did worse on a short behavioral task asking them to determine whether standard and probe durations were the same or different provides additional support for this conjecture. Whereas the processes that allow behavioral detection may occur later for children with TD (i.e., given that the amplitude of their P2 response does not differ for behaviorally-detected and undetected gaps in the current study), the link between fully processing auditory temporal information at an early sensory level and consciously detecting it at a behavioral level may be particularly tight in children with ASD.

In general, the ability to detect a brief silent gap in noise reflects the ability of the brain to detect and respond to rapid on-off-on sequences within an auditory stream. Thus, the differences we observed in the ERP response to near-threshold gaps in ASD suggest broader difficulties responding to auditory events that occur in rapid temporal sequence. Oram Cardy et al. (2005b) have reported findings in support of this notion following their examination of the M50 and M100 responses to paired auditory stimuli separated by a 150 ms gap. Whereas no group differences were seen between children with ASD and TD in either the M50 or the M100 response to the first tone within the pair, significantly fewer children with autism showed an M50 response to the second tone. This result approached significance for the M100 response as well. Thus, children with ASD were unable to produce a robust response to a second "on" stimulus, following a brief "off" interval. Interestingly, Oram Cardy and colleagues (2005b) also observed this pattern in children with Specific Language Impairment, which supports the correlational findings we reported in Study I, wherein rapid auditory processing deficits may be most associated with language difficulties in ASD. The specific components affected in ASD differed in results from the current study and from Oram Cardy et al. (2005b). However, this

discrepancy could be related to the complexity of stimuli or to the length of the silent interval, which was still almost two orders of magnitude shorter in the current study. Nonetheless, findings from Oram Cardy and colleagues converge with our findings in indicating impaired neural capacity for children with ASD to process a second sound stimulus after a short silent interval. Behavioral gap detection threshold findings from Study I and from Bhatara et al. (2013), as well as auditory temporal order judgment findings from Kwakye et al. (2011), are all also consistent with this conceptualization of ASD.

Brain structures implicated. Both the prolonged N1 and reduced P2 responses to behaviorally-undetected near-threshold gaps in ASD point to differences in brain responses originating in auditory cortex. The N1 component has generators in primary auditory cortex and the superior temporal plane (Kayser & Tenke, 2006; Vaughan & Ritter, 1970). The P2 component is associated with sources in auditory association areas and planum temporale (Godey, Schwartz, de Graaf, Chauvel, & Liégeois-Chauvel, 2001). In general, this is consistent with the notion (hypothesized in Study I discussion) that temporal processing deficits in ASD may be secondary to impairments specific to the auditory system, rather than resulting from diffuse deficits in processing timing information that also happen to impact auditory function. The ERP results of this study may be consistent with differences in more specific brain regions that have been implicated previously in ASD, as described below.

The marked reduction of P2 amplitude to behaviorally-undetected near-threshold gaps is of particular interest based on substantial evidence that a main generator of the P2 response is located in the planum temporale (Crowley & Colrain, 2004), which has been shown in fMRI studies to be involved in processing rapid temporal information in the auditory signal (Vigneau et al., 2006). Some evidence exists that N1 generators may be located in the planum temporale,

as well (Godey et al., 2001). In the left hemisphere, the planum temporale is the location of Wernicke's area, which is associated with processing and understanding of spoken language (Griffiths & Warren, 2002). Atypical planum temporale asymmetry and reduced left hemisphere planum temporale volume have been reported in both children (Rojas, Camou, Reite, & Rogers, 2005) and adults (Rojas, Bawn, Benkers, Reite, & Rogers, 2002) with autism. Deficient neural response generated from this region during detection of minute silent gaps would be consistent with behavioral results reported in Study I, which linked higher auditory gap detection thresholds to receptive language impairments in children with ASD.

It has also been noted that the P2 response may reflect, at least in part, auditory output of the reticular activating system (RAS) (Griffiths & Warren, 2002). The reader may recall from the stimulus onset findings that differences in P1 response to auditory stimulus onset might also be related to atypical activity in the RAS. Thus, the combination of findings of early but diminished P1 response to initial stimulus onset and diminished P2 response to undetected silent gap intervals in ASD could, together, point to abnormalities in the RAS in ASD. Indeed, it has long been speculated that abnormalities in the RAS could result in perceptual inconstancy (Ornitz & Ritvo, 1968), which could in turn underlie widespread symptoms associated with ASD. The RAS modulates arousal and alertness (Steriade, 1996), and Engel and Singer (2001) have proposed that sensory awareness is dependent on RAS function, and will not occur if arousal and alertness are deficient. Thus, if the ability of individuals with ASD to detect rapid temporal changes in auditory stimuli were secondary to atypical RAS function, this would suggest that, rapid temporal changes in auditory input might not be consciously detectable because of vulnerabilities related to arousal and alertness, rather than their not being physically detectable because of impaired timing mechanisms. The combination of normal N1 amplitude and markedly

diminished P2 amplitude to behaviorally undetected 3ms gaps in children with ASD could reflect this process.

Strengths, limitations, and future directions. This study has a number of strengths. As with Study I, it included a carefully characterized clinical sample, and a well-matched typically developing control group. Second, it was limited to a narrow age band of participants, which is important given that the latency of ERP responses shift with age (Johnstone, Barry, Anderson, & Coyle, 1996). Third, this study was quite rigorous in including only children with ASD who were free of psychotropic medication use. This feature allowed us to avoid the confound present in a majority of studies with clinical populations, wherein it is impossible to say with certainty whether differences in brain activity are a function of the disorder itself, or whether they are an artifact of differing medication status between groups. Fourth, concurrent behavioral measures were obtained as EEG data were collected, and behavioral performance largely did not differ between groups. This observation enables us to conclude that differences in the neural response between groups are not driven by differences in task performance, but rather, reflect real differences in the brain activity associated with equivalent behavioral performance. Finally, this study utilized relatively long duration stimuli, which allowed us to examine both the timing of the initial brain response to repeated sound onsets, and the subsequent neural response to rapid temporal events that occurred within these sounds.

This study has several limitations that warrant further analyses and follow-up in order to clarify and strengthen the results reported here. First, although the 3ms gap condition was close to the gap detection threshold observed for both groups (as indicated in Study I) and demonstrated the expected differences in ERPs, gap sizes for the task in Study II were pre-selected rather than customized for each individual's particular gap detection threshold.

Customizing ERP procedures based on the results of the initial psychophysical task could have allowed for more precise examination of the neural response to at-threshold gap intervals. Nevertheless, the present study was successful in demonstrating the feasibility of identifying group differences in neural processes associated with detecting near-threshold auditory events. Including subject-specific gap durations in future studies would increase specificity of the results reported here.

Second, following exclusion of participants for behavioral performance and motion artifact, this study may have been underpowered to detect significant group differences. The presence of moderate effect sizes in the context of near-significant *p*-values suggests that, with a larger sample size, we might detect more significant findings in line with those reported here. Third, residual noise can still be seen in grand average plots; thus, it is possible that individual subject data needs to be further pre-processed with additional filtering and/or trial-by-trial manual artifact detection. Alternatively, since some of the noise seen in the grand average plots is in the alpha band range, it is possible that participants may have become tired or bored during the task. Modifying the paradigm to include more frequent breaks may offset this limitation in the future, likely leading to cleaner average waveforms, where noise and variability detracts less from detection of significant effects.

Fourth, the choice was made to segment stimulus epochs at the initial onset of the white noise stimulus in order to look at both the neural response to initial onset and the neural response to the silent gap. However, given the extended length of the white-noise stimulus, substantial signal drift occurred following the initial response to stimulus onset. Thus, waveforms were significantly variable (i.e., were often non-overlapping) and well below pre-stimulus baseline in the 100ms prior to gap onset. As a result, comparisons across conditions and groups for the post-

gap interval may be confounded by pre-gap variability. Additional analyses with a new baseline period directly preceding gap onset may resolve this problem, and perhaps lead to more robust statistical results.

Fifth, ERP studies of gap detection using similar tasks, age range, and clinical population are relatively few, which made a priori selection of scalp locations and temporal windows for components of interest more challenging. While we selected the most canonical locations and time windows for our components of interest, they have been determined largely in typical, adult participants. Additional analyses, such as whole brain analysis using false discovery rate corrections for multiple comparisons, could result in more precise identification of the electrodes and temporal intervals that would be most informative for this dataset. Nonetheless, the scalp locations we determined using sPCA and the temporal windows we examined based on canonical locations combined with visual inspection of our data did reveal several statistically significant and/or moderately large effects.

Despite these limitations, results of Study II suggest differences between children with ASD and TD, both in their neural response to the onset of a white noise stimulus, and in their brain response to a near-threshold silent gap. These findings provide neurophysiological evidence in support of behaviorally-observed rapid auditory temporal processing deficits in ASD, as reported here in Study I and described elsewhere in previous studies. With regard to the ERP response to near-threshold silent gaps, though children with ASD and TD did not show differences in the behavioral accuracy with which they detected 3ms gaps, at a neural level, individuals with ASD showed delayed detection and reduced modulation of attention to 3ms gaps in noise on trials where they failed to detect the presence of the gap behaviorally. This finding is generally consistent with our findings from Study I regarding increased gap detection

thresholds, or less reliable detection of barely-perceptible gaps, in individuals with ASD. Clinically, it could relate to impaired ability to process language, which involves detection of equally brief temporal gaps in stimuli, which occur repeatedly and in rapid sequence over time.

Overall, results of this study suggest that a delay in the initial detection and processing of rapid temporal changes in auditory stimuli, followed by a reduction of attention orienting and perceptual classification of these changes, results in impaired ability to fully process and perceive brief temporal events within auditory input. Future studies should seek to replicate the present findings, perhaps using stimuli with gap intervals customized to each participant's individual gap detection threshold. Moreover, they might shorten the interval between initial stimulus onset and the onset of the silent gap to determine the extent to which diminished ability to process and detect the gap may be secondary to alterations in the neural response associated with the preceding stimulus or event. In addition, future studies utilizing functional MRI during auditory gap detection procedures could be useful for clarifying the anatomical source of rapid temporal processing deficits in the auditory domain observed across both Study I and Study II. With these studies, it will become increasingly possible to determine the mechanism by which, and the anatomical location in which, auditory temporal processing goes awry in ASD.

CHAPTER IV

General Discussion

This set of studies was conducted in order to further clarify the extent of rapid auditory temporal processing deficits in children with ASD using a psychophysical gap detection thresholding task. Electrophysiological methods were also incorporated in order to examine neural processes that may be contributing these deficits. Results of psychophysical procedures reflected increased auditory gap detection thresholds for broadband stimuli in ASD. ERP responses to near-threshold gap stimuli revealed reduced P2 amplitude in ASD, whether or not the gap was behaviorally detected. Where near-threshold gaps were not detected, individuals with ASD showed more marked reductions in the P2 response, following significantly delayed N1 responses. ERP findings are consistent with delayed detection of, and reduced direction of attention toward, barely-perceptible temporal changes in auditory stimuli.

Overall, results are consistent with an auditory temporal processing deficit in ASD. Gap detection in broadband noise relies on the ability to detect discontinuity in an otherwise continuous signal (Phillips, Taylor, Hall, Carr, & Mossop, 1997). Thus, our ERP results suggest that, at a perceptual level, individuals with ASD have more difficulty modulating attention toward, and correctly classifying, minute discontinuities in broadband noise. Moreover, this deficit appears to be more pronounced when earlier sensory processes associated with the initial detection of the gap are delayed. Abnormalities in the early sensory and perceptual responses to near-threshold silent gaps in noise likely contribute to reduced conscious awareness of, and ability to behaviorally detect, rapid temporal changes in auditory stimuli. This possibility is

consistent with our psychophysical results, which indicated that children with ASD require longer silent gap durations than do children with TD in order to reliably detect the presence of brief gaps in sound.

Auditory Temporal Processing and Language Deficits in ASD

Results of this set of studies provide new evidence in support of a rapid temporal processing deficit for auditory information. These findings are consistent with a growing body of literature derived from both behavioral and electrophysiological studies that has reported abnormalities in the response of individuals with ASD to rapid temporal changes, both within and between auditory stimuli (Foss-Feig et al., 2012). Impaired processing of *temporal* aspects of auditory input contrasts, at least in part, with findings of relatively intact processing of pitch-related information in auditory stimuli. Deficits in processing of speech sounds, as well as higher-level impairments in phonological processing and language comprehension are among the most commonly described audition-related findings in ASD. The capacity to perceive rapid temporal cues is fundamental for the ability to distinguish speech sounds and accurately parse the speech stream. Therefore, given that language processing deficits are so salient in the ASD population, it is perhaps intuitive that rapid temporal processing deficits would exist as well. The current study's findings support this notion. Thus, understanding the nature and extent of deficits in the processing of low-level temporal information carried in auditory stimuli may be critical for clarifying mechanistic abnormalities that underlie clinically-observable symptoms.

Results of the first study presented here demonstrated a significant relation between impaired gap detection thresholds and weaker phonological processing and receptive language skills in children with ASD. This finding supports the notion that auditory temporal processing

deficits in ASD contribute to language-related clinical impairments. Results of the second study revealed atypical neural response to miniscule temporal gaps in auditory stimuli, which supports the notion that the neural processes specifically attuned to processing of rapid auditory temporal information are disrupted in ASD. Though our spatial PCA results did not seem to suggest lateralized responses in the current study, other studies have shown that processing of rapid temporal changes in auditory stimuli is left-lateralized and localized primarily in the auditory cortex (Zaehle et al., 2004). In addition, group differences in the P2 response following near-threshold gap detection trials implicated possible deficits originating in the planum temporale, which has been shown to be specialized both for processing of rapid auditory information and for speech perception and comprehension (Vigneau et al., 2006). Thus, both our psychophysical and electrophysiological results support a role for rapid auditory temporal processing deficits in contributing to speech and language impairments among children with ASD.

Core Temporal Processing Deficits in ASD?

Theoretical models implicating temporal processing abnormalities in ASD. A number of theoretical models speculating about core deficits that might explain the full spectrum of symptoms associated with ASD emphasize the possibility that diffuse temporal processing abnormalities may be at the heart of ASD. These models can be grouped into two main categories. The first includes models that propose primary deficits related to perception of time-related information. For example, Wimpory, Nicholas, and Nash (2002) proposed that core abnormalities result from impairments in "biological clocks" that serve as temporal processors essential for processing timing information, as well as for enabling movement and communication. Allman (2011) suggested a primary deficit in processing of temporal

information across brief and prolonged time scales, which could theoretically drive atypical processing of sensory information, perceptual abnormalities, and reductions in temporal synchrony that would affect social interactions. In addition, cerebellar abnormalities have been considered a hallmark feature of ASD (Amaral, Schumann, & Nordahl, 2008, for a review), which suggests a key role for temporal processing abnormalities, as the cerebellum is central to timing-related processes, including representation of temporal information in the context of perceptual tasks (Salman, 2002).

The second group of theoretical models conceptualizes temporal processing abnormalities in ASD slightly differently, suggesting that deficits in rapid communication among brain structures and precise temporal coordination of neural activity may underlie the broad pattern of abnormalities associated with ASD. Along these lines, the temporal binding hypothesis (Brock et al., 2002) was first to suggest that ASD is characterized by reduced temporal coupling of neural responses between local networks, resulting in difficulty with integrative processes. This model was later revised to frame temporal binding deficits in the context of disordered connectivity (Rippon, Brock, Brown, & Boucher, 2007), which is in line with other theoretical models positing atypical neural connectivity as a central feature of ASD (Belmonte, 2004; Just, Cherkassky, Keller, & Minshew, 2004). In general, these theories point to abnormalities in the functioning of integrative circuits, which rely structurally on rapid transmission of signals between brain regions and, functionally, on precise temporal correlation of brain response patterns across more distant regions. While these models do not primarily implicate altered perception of temporal information related to processing of external stimuli, they nonetheless converge in proposing a primary deficit related to timing in ASD.

Cautious support for temporal processing deficit models of ASD. The present findings support the notion of timing-related deficits in ASD, albeit perhaps not in the diffuse way implied by the models just summarized. For example, we found deficits in the detection of silent gaps within auditory stimuli, a classic index of rapid temporal processing deficits, which would be consistent with models implicating aberrant perception of timing-related information. In addition, we found both delayed and reduced neural responses to near-threshold gap interval, which were associated with failure to behaviorally detect a very brief event (i.e., silent gap) occurring within the broader auditory signal. This finding provides some support for the second group of theoretical models suggesting poor temporal coordination of neural activity, in this case happening to result in reduced ability to resolve timing information within stimuli. However, we also saw *faster* latency of early sensory responses to onset of broadband noise in ASD, which is consistent with clinical observations of hyper-sensitivity to auditory events, but inconsistent with the notion of diffuse deficits in the timing of the brain response in this disorder. Thus, the specificity and applicability of all models positing a central role for temporal processing abnormalities in ASD remain to be honed, and necessitate additional studies to test directly the degree to which theories fit experimental evidence. Alternatively, it is possible that temporal processing abnormalities may be central to the clinical presentation of a subset of individuals with ASD; therefore, it could be interesting to examine whether the relative importance of timing deficits might help parse the heterogeneous phenotypes currently lumped under the ASD diagnosis.

We previously reported an extended temporal window within which task-irrelevant auditory stimuli influenced performance on primarily visual tasks for children with ASD (Foss-Feig et al., 2010; Kwakye et al., 2011). These findings provided early support for temporal

binding deficits in ASD, and suggested that temporal processing abnormalities affect multisensory functioning in ASD as well. On one hand, this finding can indeed be seen as evidence in support of theoretical models of ASD that implicate deficits in tight temporal coordination of neural responses, as integration of cross-modal sensory input was less precisely temporally coupled and bound in children with ASD compared to those with TD. On the other hand, the ability to integrate and perceive more complex, multimodal sensory occurrences relies on intact functioning of individual sensory systems. In the present study, we confirmed impaired processing of rapid temporal information in the auditory modality. Thus, it is possible that the multisensory temporal integration abnormalities we observed previously could have been secondary to focal temporal processing impairments within the auditory domain that had downstream effects on cross-modal integration. In other words, the protracted time interval over which auditory stimuli influenced visual ones in our previous tasks *could* have been an artifact of poorer auditory temporal resolution in ASD. Future studies using other modality combinations or assessing the impact of visual input on performance during a primary auditory task could clarify the extent to which temporal aspects of multisensory processing are specifically impacted in ASD.

The fact that rapid visual temporal processing appears largely spared, or even enhanced (e.g., Falter et al., 2012), in ASD provides evidence contradicting the notion of widespread deficits in timing mechanisms and processes in the ASD brain. In the somatosensory domain, enhanced spatial localization of vibrotactile information was seen among adults with ASD relative to controls when stimuli were applied for short, but not long, durations (i.e., 500ms, but not 5sec) (Tommerdahl, Tannan, Cascio, Baranek, & Whitsel, 2007). Thus, there is preliminary evidence that temporal processing may not be impaired—and might even be enhanced—during

tactile stimulation as well. Combined, these findings suggest that temporal processing deficits in the auditory domain are probably not simply a consequence of abnormalities in brain regions responsible for timing in general (though it cannot be ruled out that auditory modality-specific deficits result from impaired connectivity between brain regions subserving general temporal processing and auditory brain regions). They also point to the need to refine models positing core temporal processing deficits in ASD to more accurately specify the scope of their applicability for describing core deficits and clinical manifestations of the disorder.

Possible Neural Substrates of Auditory Temporal Processing Deficits in ASD

Since temporal processing impairments do not extent uniformly to other sensory modalities, it seems most likely that rapid temporal processing deficits seen consistently in the auditory domain reflect abnormalities in brain structures primarily responsible for auditory processing. As previously mentioned, the left superior temporal lobe, including planum temporale, has been implicated previously in autism (Rojas et al., 2002; Rojas et al., 2005), and may be a possible source location for functional abnormalities resulting in impaired auditory temporal processing in ASD.

Another possibility is that auditory temporal processing deficits may arise as a function of abnormalities in lower-level brain structures that code temporal structure of auditory stimuli. Candidate structures include the lateral lemniscus, which is a tract within the auditory brainstem that codes sound onset and extracts duration information; the inferior colliculus, which is a midbrain structure that receives projections from the lateral lemniscus, responding to sounds of specific durations and processing sounds with more complex temporal patterns; or the medial geniculate nucleus of the thalamus, which is selective for specific time intervals between

sequential sounds (Purves, 2012). Some studies of auditory brain stem response in ASD (e.g., Rosenhall, Nordin, Brantberg, & Gillberg, 2003) have found prolongations of Wave V, which is thought to reflect activity in the lateral lemniscus (Møller, Jannetta, Bennett, & Møller, 1981), lending support for the possible relevance of this structure for temporal processing abnormalities in ASD. The medial geniculate nucleus, on the other hand, has been implicated in rapid temporal processing deficits associated with reading and language disorders (e.g., Galaburda, Menard, & Rosen, 1994) and could be important in ASD as well. Future research, particularly using functional MRI techniques, should aim to clarify the level at which auditory temporal processing deficits emerge in ASD.

Study Strengths

This study has several notable strengths, including its use of multiple methodologies, which has enabled more robust characterization of auditory temporal processing differences in ASD. By employing both psychophysical and electrophysiological methods, this study has been able to: (1) identify the presence and degree of auditory temporal processing deficits in the context of a gap detection paradigm, and (2) characterize the neural response to near-threshold gaps, shedding light on underlying sensory and perceptual processes that may contribute to decreased ability to detect brief silent gaps in sound stimuli among children with ASD. Experimental tasks employed in the current study were rigorously designed, utilizing a classic paradigm (i.e., gap detection) for assessing temporal processing abilities that also has shown sensitivity to deficits in clinical populations characterized by language-related difficulties. Moreover, the gap detection paradigm requires detection of brief temporal events within sounds, but demands little in the way of sustained attention, judgment, or other higher-order decision-

making processes that can be heavily involved in other tasks for assessing temporal processing abilities. Thus, the relatively simple perceptual discrimination required for gap detection made the tasks selected in this study particularly useful for studying children with ASD, whose diffuse social-communicative, neurocognitive, and behavioral deficits often confound their performance on tasks meant to isolate lower-level perceptual processing.

The participant sample in the psychophysical component of this study was substantial, allowing for good ability to detect differences in the measures of interest. Participants with ASD were well-characterized clinically and, in the electrophysiological component of the study, were free of psychotropic medications that might confound the ability to interpret group differences in brain responses as specific to ASD, and not secondary to group differences in medication status. Careful screening was conducted with control participants to ensure children were typically developing, and free of any learning, psychiatric, or neurological disorder. Control children also did not have close relatives with ASD, ensuring that they represented a relatively "clean" comparison sample. Across both Study I and Study II, ASD and TD groups were well-matched for age, intellectual ability, gender, and handedness, which improved the confidence with which we can assert that group differences were due to diagnostic status.

A final strength of this study was its inclusion of an array of standardized parent report and direct assessment measures of sensory, language, and social functioning. By including these measures, we were able to explore relations between markers of low-level auditory temporal processing, and indices of more clinically relevant functioning. The breadth of information we collected allowed us to hone in on the relevance of rapid auditory temporal processing deficits for language functioning in particular. As a result, we were able to make more informed hypotheses regarding neural substrates that might underlie observed difficulties, and to more

precisely define the role auditory processing abnormalities may play in contributing to the broader pattern of symptoms associated with ASD.

Study Limitations and Future Directions

Despite this studies many strengths, it is not without its limitations. First, all participants with ASD were high-functioning, having IQ scores at or above the average range. This selection criterion was necessary in order to ensure task comprehension and engagement. However, the IQ range restrictions prevent us from concluding whether the behavioral and neural differences detected in auditory temporal processing within the current sample would extend to children with ASD and concomitant intellectual disability. That being said, the fact that we observed significant deficits relative to TD children even in a very high functioning sample of children with ASD highlights the salience of our findings. Namely, given the relations we observed between gap detection thresholds and language processing abilities, one might expect that the auditory temporal processing deficits we identified would hold—or even be more pronounced—in lower functioning children with ASD whose language is often more limited, and at times absent. Determining whether this hypothesis is true will be a task for future research. To this end, passive listening electrophysiological studies examining the MMN response to infrequently occurring silent gaps in auditory stimuli among trains of sequential, continuous sounds might be one avenue toward evaluating the integrity of auditory temporal processing in more severely affected children with ASD.

Second, our stimuli consisted of relatively long intervals of broadband noise, with gaps delimited by leading and lagging noise bursts of close to 500ms. Stimuli were chosen for several distinct reasons. First, they were chosen based on stimuli used in the literature examining gap

detection in clinical child populations. Second, they were selected because gap detection thresholds ought to be at their lowest for broadband noise, so differences might be most salient for these stimuli. And, finally, examining gaps in pure tone stimuli necessitates using overlaid masking noise, and sound segregation may itself be impacted in ASD (Teder-Salejarvi, Pierce, Courchesne, & Hillyard, 2005), which could confound gap detection findings for pure tone stimuli in this disorder. Research has shown that the ability to detect gaps in noise is affected by the duration of the leading and lagging sound stimuli (He, Horwitz, Dubno, & Mills, 1999). Moreover, in older adults who have auditory temporal processing impairments, gap detection thresholds increase more drastically than in younger adults as the duration of the delimiting sounds decreases (Schneider & Hamstra, 1999). Short duration leading and lagging stimuli are likely most similar to those that enclose temporal gaps in speech, so impairment under these conditions could have more drastic effects on speech perception, and perhaps on language function more broadly. Future research examining auditory gap detection abilities in ASD using shorter stimuli with more brief leading and lagging sounds could potentially illuminate more striking impairments than those observed here. However, the fact that we observed deficits in the ability of children with ASD to detect silent gaps even with longer leading and lagging noise bursts highlights the extent to which processing of rapid timing events in auditory stimuli is likely stable and pervasive in this disorder.

Related to the previous observation, research has shown that gap detection thresholds increase if the leading and lagging sound stimuli differ from one another. That is, if a silent gap is delimited by spectrally different markers, gap detection ability decreases and longer duration gaps are needed in order to reliably detect their presence (Phillips et al., 1997). This phenomenon is thought to be due to the fact that detecting gaps between differing sounds requires comparison

of information between more than one perceptual channel, whereas detecting gaps in an otherwise continuous sound stimulus requires only detection of discontinuity within a single channel (Phillips et al., 1997). Our findings speak only to within-channel gap detection abilities, whereas between-channel gap detection may be more tightly linked to the temporal processing that occurs during speech perception, and therefore perhaps more impaired in ASD (Formby, Barker, Abbey, & Raney, 1993). Moreover, since ASD is thought to be characterized by reduced ability to integrate information across local circuits (e.g., Brock et al., 2002), one could speculate that between-channel gap detection might be particularly impacted in ASD from a mechanistic standpoint as well. Thus, in addition to examining gap detection abilities in the context of shorter duration leading and lagging sounds, future research targeting ASD should examine detection of silent gaps between spectrally-dissimilar leading and lagging sounds. These two lines of research could build upon the results observed here by contributing to a more comprehensive understanding of the extent to which temporal processing deficits affect perception in children with ASD.

Third, though our choice of electrophysiological methods to explore the brain basis of auditory temporal processing differences in ASD allowed us to very precisely examine the time course of the neural response to silent gaps in noise, it limited our ability to assess the spatial localization of observed differences in the brain. Instead, we were only able to speculate about possible brain structures that could be affected in ASD during performance of our tasks. Future studies employing fMRI approaches during auditory gap detection could offer clarification regarding specific brain regions that are impacted in ASD in the context of auditory temporal processing for non-speech stimuli. Such studies could directly examine whether brain structures hypothesized to underlie the current study findings are indeed involved in the processes we

assessed. Gaining this information would improve our understanding of the neuroanatomical origin of deficits observed here, as well as suggest what other cognitive processes they may relate to, or what additional functional significance they may hold, dependent on where in the brain they arise.

Fourth, this study focused on rapid temporal processing abilities in the auditory modality only. As discussed in Chapter II, literature examining visual temporal resolution and rapid accumulation of visual information point to intact, or even enhanced, temporal processing in the visual modality. Comparisons across studies are informative, and suggest a possible dissociation between the integrity of temporal processing in the auditory and visual modalities. Nevertheless, it would be most helpful if studies used analogous measures to test auditory and visual temporal processing in parallel, within a single sample of participants with ASD. In line with this recommendation, in our previous study of temporal order judgment abilities in children with ASD, we were able to show deficits in the auditory domain in the context of intact visual performance (Kwakye et al., 2011). However, additional studies taking this approach, and perhaps also incorporating assessments of other sensory modalities, will be helpful in determining the extent to which temporal processing deficits are specific to auditory functioning. Clarifying the specificity of these deficits will inform more clear hypotheses as to the neural substrates and underlying processes likely to be driving results such as those seen in this study.

Clinical Implications and Translational Value

The results of this study shed light on low-level differences in sensory processing that appear to contribute to clinically-observable differences in reactivity to auditory stimuli and in processing of phonological and higher-level language information. Specifically, earlier latency of

the brain's response to auditory stimulus onset is consistent with hyper-sensitivity to sounds, whereas reduced magnitude of its response—both to sound onsets and to brief silent gaps in ongoing noise—fits with clinical reports of hypo-reactivity to auditory input, such as poor response to name. The significant relation between auditory gap detection thresholds and standardized assessment scores related to phonological and receptive language abilities supports the notion of temporal processing impairments as a potential underlying deficit contributing to core features of ASD related to impaired language and communication function. By better understanding auditory temporal processing deficits in ASD, we may gain better understanding of core deficits fundamental to the broader array of symptoms associated with the ASD phenotype. This, in turn, might lead to earlier detection of ASD as audition comes on-line in utero (Busnel, Granier-Deferre, & Lecanuet, 1992) and deficits in auditory processing may be detectable long before deficits in social and communicative behaviors are clearly observable.

If rapid temporal processing impairments indeed contribute to difficulties with processing language for children with ASD, many possible translational implications emerge. These could include targeted training to improve auditory temporal processing, as well as modification of how auditory information is presented to children with ASD in order to accommodate their temporal processing weaknesses. To the former point, two studies have shown that interventions targeting low-level temporal processing abilities can be effective among children and adults with related deficits. First, in a group of school-age children with language-based learning deficits, Merzenich and colleagues (1996) applied specially-developed auditory-visual "games" that trained children, over many repeated learning trials, to respond to stimuli of increasingly fast frequency-modulation, occurring at increasingly short inter-stimulus intervals using adaptive training procedures. After a course of training sessions, performance levels of

children with language impairments improved drastically, at times to the level of typically developing children. Most importantly, this generalized to improved performance on unrelated behavioral tasks related to temporal processing and phonetic element recognition ability. Though the extent to which these training-driven improvements in temporal processing and phoneme recognition generalized to children's ability to process linguistic information in more naturalistic contexts was not tested, one can envision that effective training programs targeting underlying processing deficits could have significant impact on everyday functioning. Second, in a group of three adults with dyslexia, intensive training using the *Fast Forward* protocol (Scientific Learning, Berkeley CA) normalized brain activation during a task assessing processing of rapid non-speech analogues (Temple et al., 2000). Specifically, employing adaptive training designed to improve successive processing of both linguistic and non-linguistic stimuli led to increased activation in left prefrontal cortex, as well as measureable improvement on tests of rapid auditory processing and oral language comprehension. Though the efficacy of these types of interventions has not always borne out in the dyslexia literature, similar training programs might be more effective in improving rapid auditory temporal processing among children with ASD, particularly if the neural basis of temporal processing deficits differs between ASD and other disorders. If effective, these interventions may have the ability to impact both language functioning and the ability of children with ASD to respond appropriately, yet not over-react, to sound.

Modifications can be envisioned for altering how oral language information might be presented to children with ASD in order to accommodate temporal processing deficits. For example, speakers could slow down the overall pace of their speech, which would presumably elongate temporal features of speech (e.g., acoustic cues by which phonemes are distinguished,

silent gaps denoting phonetic and syntactic structure including syllable parsing and demarcation of words and sentences within the speech stream). One can envision that, by doing this, rapid temporal features of speech would become more detectable to individuals with ASD, which could in turn improve their ability to perceive the speech stream accurately and comprehend the linguistic content, as a result.

Along these lines, another possibility might be to increase use of speech having characteristics similar to "motherese" with children with ASD. "Motherese" is infant-directed speech that is characterized by higher pitch, but also slower pace, longer pauses, and exaggerated intonation contours (Grieser & Kuhl, 1988). For infants, the pitch contour of motherese seems to be the feature that is most salient and attention-grabbing (Fernald & Kuhl, 1987); however, the temporal features of motherese could make use of similar speech patterns appropriate for circumventing auditory temporal processing deficits in ASD. The effectiveness of motherese with children with ASD has been noted previously. For example, severely delayed children, many of whom had autism, showed increased responsiveness to motherese relative to more typical conversational voice patterns (Santarcangelo & Dyer, 1988). Moreover, it has been reported that withdrawn infants who later develop autism may be more responsive to motherese (Mahdhaoui et al., 2011). This observation led these researchers to speculate that, because of their lack of interactive responsiveness, children with autism may have less repeated exposure to motherese, which is important for both language and social development (Fernald, 1985). Thus, it may be worth considering whether intentional, frequent, and prolonged use of speech sharing similar temporal acoustic characteristics to motherese may improve the responsiveness of children with ASD to language, given their apparent rapid auditory temporal processing deficits.

In sum, increasing our understanding of auditory temporal processing impairments may have clinically significant impact for several reasons. First, it may elucidate some of the underlying deficits driving core clinical features of ASD. Specifically, it may lead to an improved understanding of the central social, communication, and behavioral deficits associated with ASD, along with increased awareness of concomitant sensory, perceptual, and cognitive differences experienced by individuals with ASD. Second, it may contribute to our understanding of the neural underpinnings of ASD, potentially offering new targets for pharmacological interventions and contributing to a better understanding of the biological etiology of this disorder. Third, it may help distinguish deficits that are unique to ASD (or even a subset of individuals with ASD), which could improve clinicians' ability to differentiate among developmental disorders, thereby increasing diagnostic accuracy. Fourth, it may enable earlier detection of ASD by pointing to deficits in processes that are both rapidly developing and experimentally assessable even in neonates. And, finally, it may lead to new interventions, or novel use of existing ones, that stand to improve the ability of children with ASD to process language effectively. For all these reasons, further research clarifying the nature and extent of auditory temporal processing deficits in ASD is warranted.

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