Neural Correlates of Auditory Processing and Language Impairment in Children with Autism Spectrum Disorders

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Table of Contents

Thesis summary

The term autism spectrum disorders (ASD) refers to a group of neurodevelopmental disorders characterised by social and communication impairments, as well as restricted and repetitive patterns of behaviour. The thesis contains four studies using magnetoencephalography (MEG) to measure brain responses to auditory stimuli. The aim is to better understand the neural correlates of auditory processing deficits in ASD, and determine how such deficits may be associated with spoken language impairment that affect many individuals on the autism spectrum.

In **Study 1**, we tested six- to 13-year-old children with ASD. We determined that a child's language ability predicted how similar their brain responses to speech and nonspeech sounds were to those of similar-aged typically developing (TD) children, suggesting that language impairment in ASD may be linked to brain immaturity.

Study 2 was a case study of a nonverbal girl with ASD, using the same procedures as Study 1. She showed a strong evoked response to nonspeech and a significantly weaker response to speech – this pattern of results was not found in any of the children tested in Study 1. Results demonstrate the potential of MEG for future studies of severely affected children with ASD who are usually excluded from functional neuroimaging research.

In **Study 3**, we developed the magnetic acoustic change complex (mACC) as a neural measure of auditory discrimination. We tested 15 normal hearing adults on the mACC and the mismatch field (MMF), a more commonly used measure of auditory discrimination. The mACC had higher signal to noise ratio than the MMF, suggesting that it may be an efficient index of auditory discrimination for testing child and clinical populations.

Study 4 used the mACC paradigm to measure auditory discrimination of vowel and pitch changes in five- to 14-year-old children with ASD. On average, the children with ASD had significantly weaker mACC responses than age-matched TD controls. However,

there was no significant association between mACC amplitude and spoken language scores. The study provides evidence of impaired auditory discrimination in ASD and demonstrates the potential of this paradigm for future studies of ASD.

Statement

I certify that the work in this thesis entitled “Neural Correlates of Auditory Processing and Language Impairment in Children with Autism Spectrum Disorders” has not previously been submitted for a degree, nor has it been submitted as part of requirements for a degree to any other university or institution other than Macquarie University.

I also certify that the thesis is an original piece of research and it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself has been appropriately acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis. The research presented in this thesis was approved by the Macquarie University Ethics Review Committee, reference numbers: **HE23NOV-R05540**; **HE28NOV2008-R06249**; **5201200658** and by Autism Spectrum Australia (ASPECT), reference number: **1217**.

Signed:

Shu Hui Yau (Student Number: 42187087)

9 May 2014

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work with, and without whom, this research would not have been possible.

Thank you all from the bottom of my heart.

Chapter 1

General Introduction

GENERAL INTRODUCTION

Autism Spectrum Disorders

The term autism spectrum disorders (ASD) refers to a group of neurodevelopmental disorders that manifest themselves in early childhood and are characterised by social and communication impairments, as well as restricted and repetitive patterns of behaviour (APA, 2000, 2013; WHO, 1992). In Australia, diagnosis of ASD is typically conducted according to criteria set out in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Children with ASD in the studies that comprise this thesis had diagnoses of either Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) as described in the fourth edition of the manual, DSM-IV. Under DSM-IV, Autistic Disorder was diagnosed in the presence of six or more of the 12 behavioural symptoms that are shown in Table 1. They had to meet at least two criteria from the "social" domain and at least one criterion from the "communication" domain as well as the "repetitive and restricted behaviours" domain. Individuals who failed to meet criteria for Autistic Disorder might be diagnosed with Asperger's Disorder or PDD-NOS. Asperger's Disorder was defined in terms of social impairment and repetitive and restricted interests but with typical language development. Criteria for PDD-NOS included the presence of social impairment and either communication impairment or repetitive and restricted behaviours (but not both).

Table 1

Diagnostic Criteria Outlined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for Autism Spectrum Disorders (ASD). Six or more criteria need to be met for diagnosis of ASD.

Domains	**Criteria**
Restricted, repetitive, and stereotyped patterns of behaviour. Manifested by at least *one* of the following:	1. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus. 2. Inflexible adherence to specific, non-functional routines or rituals. 3. Stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements). 4. Persistent preoccupation with parts of objects.
Communication impairment. Manifested by at least *one* of the following:	1. Delay in, or total lack of, the development of spoken language not accompanied by an attempt to compensate through alternative modes of communication such as gestures or mime; in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others. 2. Stereotyped and repetitive use of language or idiosyncratic language. 3. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level.
Social interaction impairment. Manifested by at least *two* of the following:	1. Marked impairment in the use of multiple nonverbal behaviours (e.g. eye gaze, facial expression, body postures, and gestures) to regulate social interaction. 2. Failure to develop peer relationships appropriate to developmental level 3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. lack of showing, bringing, or pointing out objects of interest). 4. Lack of social or emotional reciprocity.

A new edition of the DSM (DSM-V) was published mid-2013. In this version of the DSM, social and communication impairments were merged into a single domain, and the three separate diagnoses of Autistic Disorder, Asperger's Disorder, and PDD-NOS were rolled into a single category of ASD. This is consistent with the diagnosis of ASD in this thesis. Indeed, DSM-V explicitly states that individuals with any of the three diagnoses under DSM-IV should automatically qualify for an ASD diagnosis under DSM-V.

The term ASD implies a "spectrum" of severity. However, this underplays the complexity and heterogeneity of clinical manifestations of behaviour within the diagnostic (represented by the blue circles in Figure 1) and non-diagnostic features (represented by green boxes in Figure 1). Indeed, Geschwind and Levitt (2007) have argued that ASD should be renamed "the autisms" rather than being considered as a single entity. Alternatively, Happé, Ronald, and Plomin (2006) have argued that features of ASD might be inherited independently and hence should be studied separately. In line with this school of thought, the aim of this research program was to better understand the origins of the heterogeneous spoken language abilities in children with ASD.

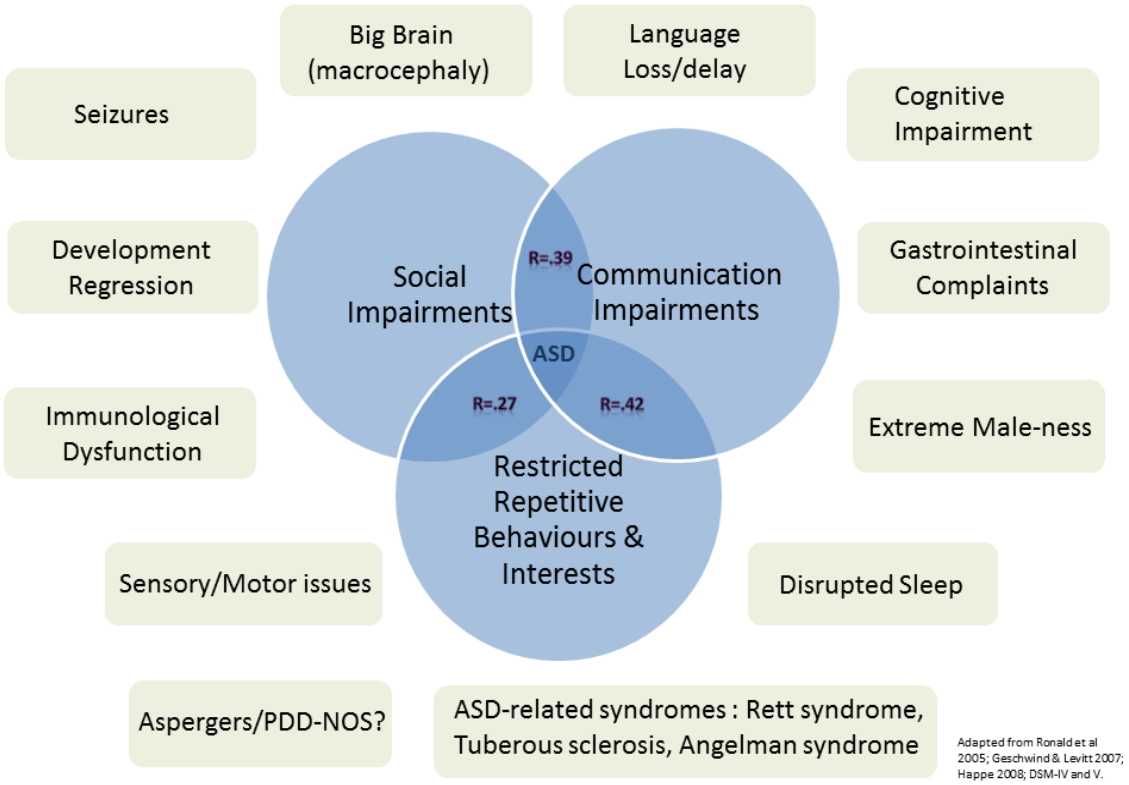

Figure 1. Heterogeneity in Autism Spectrum Disorders (ASD). R values show low to moderate correlations between each major clinical symptom in the ASD 'triad' for school-aged boys (Happé, 2008). Correlations for girls are lower. Green boxes surrounding the triad of impairments (blue circles) include symptoms and issues commonly reported and related syndromes.

Language Impairment in ASD

The language abilities of individuals with ASD vary widely, ranging from mutism, to minimal functional use of language, to near-typical language with few impairments in semantic and pragmatic language use (Boucher, 2003; Jarrold, Boucher, & Russell, 1997; Rapin & Dunn, 2003; Tager-Flusberg, Edelson, & Luyster, 2011; Tager-Flusberg & Kasari, 2013; Tager-Flusberg, Paul, & Lord, 2005). In his influential 1943 paper, Leo Kanner described abnormal communication abilities in a group of 11 children with

"autistic disturbances in affective contact". This group included children with a range of language impairments; some of whom (1) were ostensibly mute but would occasionally say a full sentence; (2) had echolalia, pronoun reversal, off-tangent speech; (3) were generally unresponsive to questions; and (4) appeared to have no motivation to communicate. For the next 40 years, such language difficulties and atypicalities were considered cardinal features of autism, and were proposed by some researchers to be the primary cause of the other symptoms of the condition (Rutter & Bartak, 1971). In the DSM-III published in 1980, "gross deficits in language development" were a necessary criterion for diagnosis of Infantile Autism. However, the following year, Lorna Wing published an influential article, describing individuals with what became known as Asperger's syndrome (Wing, 1981). These individuals demonstrated social difficulties similar to those with more traditionally recognised forms of ASD, but had no history of language impairment. Asperger's syndrome was first included as a separate diagnosis in DSM-IV and, as noted above, has been folded into the ASD category in DSM-5. Consequently, language impairment is no longer considered a diagnostic feature of ASD. Instead, it is now one of the greatest sources of heterogeneity within the ASD population.

The development trajectory of spoken language of children with ASD can be unusual. Around 15 to 40% of toddlers with ASD are reported to experience a loss or regression of verbal and nonverbal communication skills in the second year of their lives (Goldberg et al., 2003; Lord, Shulman, & DiLavore, 2004; Luyster et al., 2005). Fortunately, most of these toddlers seem to later regain their functional spoken language skills, at least well enough to express their needs and wants. However, the social aspects of many children's spoken language abilities often remain impaired (e.g., directing attention and reciprocal exchange). In the school years, some children with ASD continue to struggle with various aspects of language. Many school-aged children with ASD have phonological and syntactic impairments similar to those seen in children with specific

language impairment (SLI). It has therefore been suggested that a subtype of ASD overlaps with specific language impairment (SLI; Kjelgaard & Tager-Flusberg, 2001; Tager-Flusberg & Joseph, 2003). In support of this, Tager-Flusberg and Joseph (2003) found an SLI subgroup of children with ASD who performed poorly on a test of nonword repetition - a measure that is considered to be a sensitive marker for SLI (Bishop, North, & Donlan, 1996). However, it has also been argued that similarities between ASD and SLI may be superficial and possibly a consequence of substantial impairment in multiple ASD domains (Whitehouse, Barry, & Bishop, 2008; Williams, Botting, & Boucher, 2008).

In contrast to phonological and syntactic language impairments which might be present in a subgroup in ASD, the social aspects of language ("pragmatics") are, by definition, affected in all individuals with ASD (Frith & Happé, 1994; Tager-Flusberg, Paul, & Lord, 2005). In addition to pragmatic language impairment in ASD, there is evidence for difficulties in the more complex aspects of language such as irony, idioms, and metaphor (Anderson et al., 2007; Happé, 1995; Norbury, 2004; Tager-Flusberg et al., 2011). Even in children with "optimal outcomes" in ASD (Fein et al., 2013), or those in age-appropriate mainstream classes, there appear to be residual impairments in terms of pragmatic and semantic language (Kelley, Paul, Fein, & Naigles, 2006) that can affect functional, communicative and social outcomes later in life (Billstedt, Carina Gillberg, & Gillberg, 2007; Gillberg & Steffenburg, 1987; Szatmari, Bryson, Boyle, Streiner, & Duku, 2003).

The Relationship Between Poor Auditory Processing and Language Impairment in ASD

Atypical auditory processing is a common and widely acknowledged feature of ASD, and it is hypothesized that language impairments in ASD may arise from some kind of auditory processing deficit (Rapin & Dunn, 2003; Siegal & Blades, 2003). It has been suggested that individuals with ASD have either reduced or enhanced responsiveness to

sounds (Gomes, Pedroso, & Wagner, 2008; Khalfa et al., 2004; Rosenhall, Nordin, Sandström, Ahlsen, & Gillberg, 1999), or they may have enhanced responsiveness to some sounds (e.g., nonspeech sounds) but reduced responsiveness to other sounds (e.g., speech sounds) (Baranek, 1999; Dahlgren & Gillberg, 1989; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Gillberg & Coleman, 1996).

Reduced responsiveness to sounds

One postulation is that children with ASD have reduced ability to process the differences between sounds ("auditory discrimination"). Studies of auditory discrimination and language acquisition have suggested that the ability to discriminate between formant frequencies in speech is crucial to language development (Kuhl, 2004; Werker, 1984, 1988, 2005). Impairments in the discrimination of sounds might disrupt the formation of stable representations of speech sounds (phonemes) in the brain, which in turn may affect a child's ability to learn the phonology, syntax, and semantics of their native language through the speech of other people. Impaired discrimination may also impair the perception of prosody, which conveys emotional information and details important to social communication (McCann & Peppé, 2003; McCann, Peppé, Gibbon, O'Hare, & Rutherford, 2007; Peppé, McCann, Gibbon, O'Hare, & Rutherford, 2007).

Reduced responsiveness to social sounds

An impairment in the auditory processing of sounds could be specifically related to reduced ability or motivation to specifically process "social" sounds. Children and infants with ASD are often reported to be under-responsive towards the sound of their own name or to social initiations (Baranek, 1999; Dawson, 2004; Dawson et al.,1998; Tharpe et al., 2006). Moreoever, experimental studies have found that infants with ASD or at high risk of ASD tend to listen longer to nonspeech rather than speech stimuli (Curtin & Vouloumanos, 2013; Klin, 1991). This is not seen in typical development, where infants show a natural preference for speech (compared to matched nonspeech or environmental

sounds), which is presumed to facilitate language acquisition (Shultz & Vouloumanos, 2010; Vouloumanos & Werker, 2007).

Enhanced responsiveness to sounds.

In contrast, it has been suggested that poor spoken language in ASD may stem from enhanced sound discrimination in some individuals with ASD. This enhanced auditory processing mechanism might disrupt their ability to ignore linguistically irrelevant auditory information and impair their extraction of relevant features of speech sounds (Lepistö et al., 2008). Again, this disruption might have a cascading influence on the development of phonology, syntax, and semantics in these individuals. Consistent with this, DePape, Hall, Tillmann, & Trainor (2012) reported that individuals with ASD had less specialisation for native phonemic categorization, but higher incidences of absolute pitch, compared to the individuals with typical development (TD). Participants with ASD have also been found to have superior pitch discrimination for a variety of sounds including tones, speech, and music (Bonnel et al., 2010; Bonnel et al., 2003; DePape et al., 2012; Heaton, Hudry, Ludlow, & Hill, 2008; Järvinen-Pasley, 2008). Interestingly, recent studies have found that enhanced pitch processing is only found in individuals with ASD who have a history of language delay (Bonnel et al., 2010; Jones et al., 2009). The outcomes of these studies support the idea that enhanced sound processing skills may interfere with speech perception, which in turn may undermine language development.

Neurophysiological Measures of Auditory Processing

Testing theories of auditory processing in ASD using behavioural tests is often challenging because many individuals with ASD struggle to understand task instructions and maintain attention throughout long (and often boring) testing paradigms (Allen & Courchesne, 2001; Roberts et al., 2008). To avoid these problems, some researchers have turned to electroencephalography (EEG) and magnetoencephalography (MEG) that allow the objective measurement of auditory processing in individuals with ASD without their

overt attention (e.g., while they watched a movie). Such paradigms are often referred to as "passive" paradigms.

A strength of EEG and MEG passive paradigms over neuroimaging paradigms (e.g., functional magnetic resonance imaging) is that they both reflect brain activity in real-time with millisecond precision (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993; Hari, 2005; Roberts et al., 2008). This is particularly important for measuring the processing of sound since the acoustic features of many sounds, and particularly speech sounds, change rapidly across time. Being able to measure activity at the speed the brain works also informs us which specific part of speech perception is disrupted at the cortical level (e.g. onset of sounds, discrimination, or involuntary orientating towards a specific sound).

Electroencephalography (EEG)

An EEG is a continuous recording of the electrical activity that is emitted by large groups of neurons. This electrical activity is measured using electrodes that are placed on the scalp. In order to measure how the brain responds to a particular stimulus, an individual's continuous EEG is recorded whilst they are presented with hundreds of examples of that stimulus. Each separate EEG response to a stimulus will comprise a small proportion of signal which is related to the stimulus, compared to noise, which is unrelated to the stimulus. However, since the noise is random, the averaging of many EEG trials cancels out the random noise, leaving the signal of interest from the brain. This is called an event-related potential (ERP). An ERP waveform comprises a series of positive and negative peaks that are named after their polarity (P = positive, N = negative) and either according to their order or latency in the waveform.

Obligatory ERPs. The first three of these ERPs – the "P1", "N1" and "P2" – are often grouped together into a set called the "obligatory" ERPs (see Figure 2). In adults, passive auditory obligatory ERPs comprise a small P1 and large N1 and P2 responses

between 50 and 150 ms. In contrast, children have a larger P1 than adults and smaller N1 and P2 responses that increase in size with age (Čeponiene, Rinne, & Näätänen, 2002; Ponton, Don, Eggermont, Waring, & Masuda, 1996; Ponton, Eggermont, Kwong, & Don, 2000; Wunderlich & Cone-Wesson, 2006; Wunderlich, Cone-Wesson, & Shepherd, 2006). In both adults and children, the obligatory auditory ERPs are thought to reflect basic levels of auditory sensory encoding and detection of sound, and can be elicited by a range of speech and nonspeech sounds (Hari, 1991; Näätänen & Picton, 1987). The N1-P2 complex has been obtained to intensity and frequency changes in tones (Näätänen & Picton, 1987; Spoor, Timmer, & Odenthal, 1969; Yingling & Nethercut, 1983), syllables (Hari, 1991; Ostroff, Martin, & Boothroyd, 1998), consonant-vowel changes (Kaukoranta, Hari, & Lounasamaa, 1987; Ostroff et al., 1998) and natural speech sounds (Tremblay, Friesen, Martin, & Wright, 2003). Obligatory responses are considered to be minimally affected by attention (Näätänen, 1992), and are useful in their sensitivity to auditory processing impairments in children (Purdy, Kelly, & Davies, 2002; Tonnquist-Uhlén, 1996).

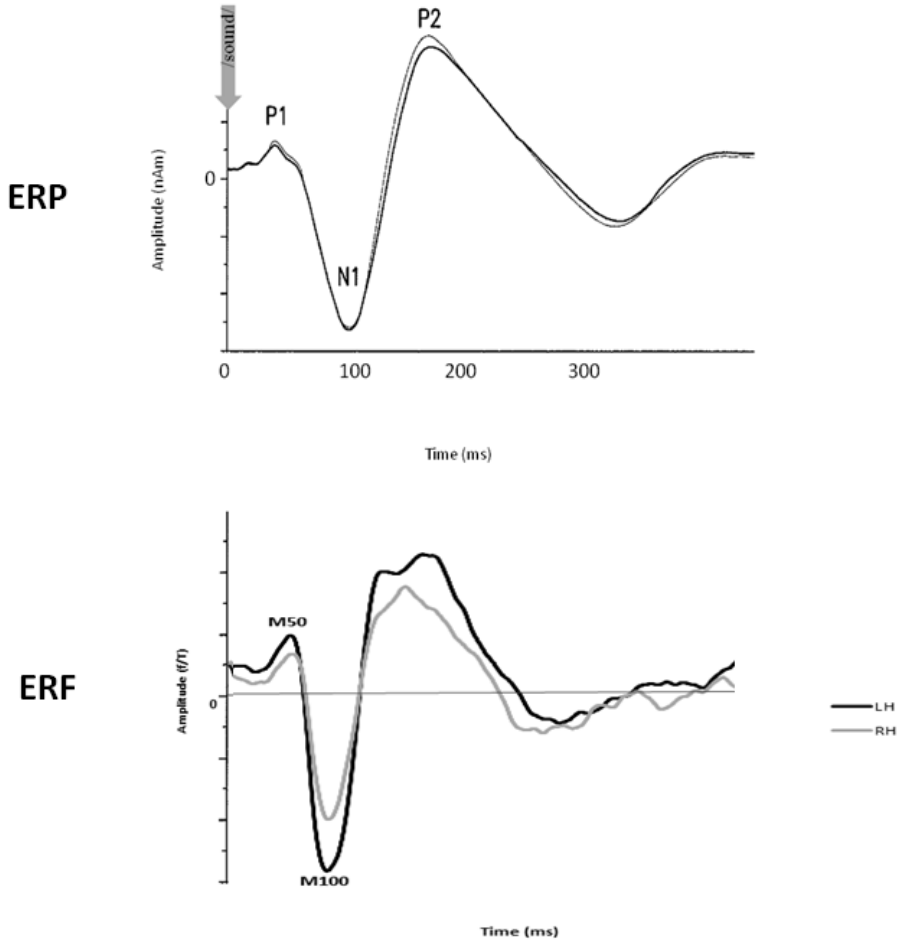

Figure 2. The top figure shows a typical adult event-related potential (ERP) P1, N1, P2 obligatory response to a tone (top figure). The bottom figure shows the corresponding event-related field (ERF) M50 and M100 obligatory responses. ERF waveforms are left hemisphere (LH) and right hemisphere (RH) source waveforms.

Mismatch Negativity. Another ERP that has been used to measure brain responses to sounds without individuals' attention is the "mismatch negativity" (MMN), which typically peaks at around 200 to 250 ms. The MMN is commonly used to measure auditory discrimination since it is triggered by a rare "deviant" sound presented amongst frequent "standard" sounds. The size of the MMN is typically measured by subtracting the ERP to

the standard sound from the ERP to the deviant sound. The MMN is reported to have multiple sources in the auditory cortex (Alho, 1995; Jääskeläinen et al., 2004), as well as in prefrontal areas of the brain (Alain, Woods, & Knight, 1998). These sources implicate several functions and interpretations of the MMN, as will be discussed in detail in Paper 3.

P300. A fifth ERP that has been commonly used to measure individuals' brain responses to sounds is the P300. The P300 is typically elicited 300 ms after the onset of a novel or distracter sound (Escera, Alho, Winkler, & Näätänen, 1998; Squires, Squires, & Hillyard, 1975). It is composed of several subcomponents (P3a, P3b, a slow wave) and its function is linked to higher cognition such as attentional orienting and memory processes (Donchin & Coles, 1988; Linden, 2005; Polich, 2007; Rogers et al., 1991). For example, the P3a subcomponent is elicited in children and adults to a novel sound within an oddball paradigm, and indexes involuntary attention switching in the brain to the novel sound (Escera et al., 2000; Horváth, Czigler, Birkás, Winkler, & Gervais, 2009; Ruhnau et al., 2013).

Magnetoencephalography (MEG)

Magnetoencephalography has been referred to as the magnetic cousin of EEG (Roberts et al., 2008). It measures the magnetic fields that circle the electrical activity generated by the flow of post-synaptic ions near the scalp surface (see Figure 3). MEG activity is recorded at the scalp using superconducting quantum interference devices, also known as SQUIDs. The brain activity picked up by the SQUIDs in MEG consists of activity from thousands of synchronously firing ("activated") neurons to a stimulus. This magnetic activity comes from activated neurons in layers 4 and 5 of the brain that are tangentially oriented or parallel to the surface of the scalp (Bagic & Sato, 2007; Hämäläinen et al., 1993; Hari, 2005; Sato, Balish, & Muratore, 1991).

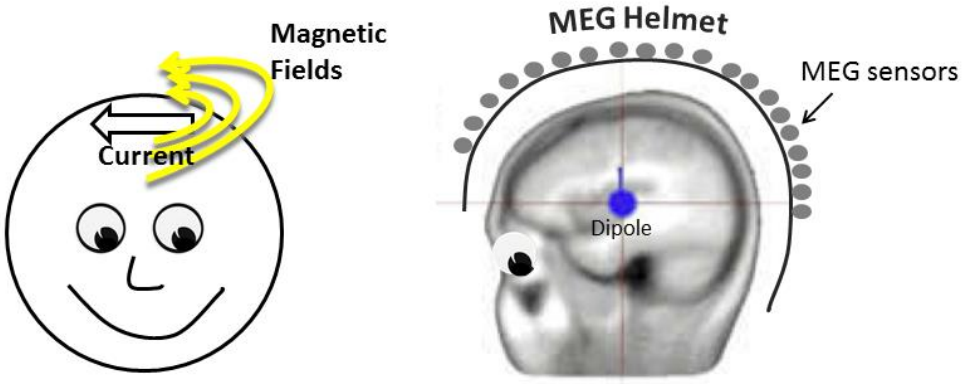

Figure 3. A schematic representation of electrical current and accompanying magnetic fields. The yellow arrows in the left figure indicate magnetic fields leaving and entering the scalp. The figure on the right shows the magnetoencephalography (MEG) helmet and sensors that pick up the magnetic fields.

MEG responses are typically measured at the level of the cortex (i.e., MEG source responses, see Figure 4). However, they can also be measured at the level of the sensors. Either way, because the signal generated in the brain to each stimulus is tiny, it is necessary to average MEG responses to many stimuli to obtain a clear waveform. With the averaging of trials, brain activity that is not time-locked to the stimulus (i.e., noise) is averaged out, leaving a waveform that is related to the stimulus of interest (i.e., signal). Averaged MEG waveforms are called event-related fields (ERFs). An ERF comprises a series of peaks that correspond to ERP peaks. Unlike ERPs, these peaks are reference-free and polarity-free and so do not comprise positive and negative peaks. Nevertheless, ERF peaks are often labelled according to ERP conventions, with "m" or "M" tagged to the start or end of the signal name (e.g. N1m, P3m). Otherwise ERF peaks are named according to their approximate latency (e.g., M100). ERFs commonly used to measure brain responses to sounds without listeners' attention are: the obligatory M50 (corresponding to the P1) and M100 (corresponding to the N1) as seen in Figure 2, the mismatch magnetic field (MMF; corresponding to the MMN), and the magnetic P3 (Näätänen & Picton, 1987;

Poeppel et al., 1996; Roberts, Ferrari, Stufflebeam, & Poeppel, 2000).

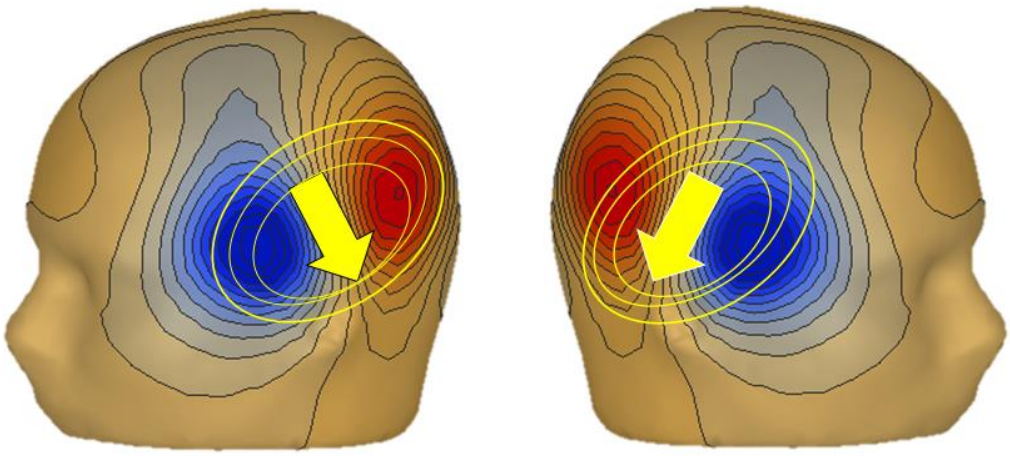

Figure 4. Magnetoencephalography (MEG) head models. Yellow arrows represent the dipoles or source of activity. Yellow circles indicate the magnetic flux entering and leaving the head in a circular manner (please imagine this in 3D). Red and blue activation maps represent the magnetic flux going in (blue) and coming out (red) of the brain as measured by MEG sensors near the auditory cortex. The goal of source analysis is to determine the activity going on in real-time in the small patch of cortex indicated by the yellow arrows.

Strengths of MEG Compared to EEG

Given that MEG ERFs produce analogous responses to EEG ERPs, one might wonder why researchers employ ERFs rather than ERPs given that MEG ERFs are so much more expensive (i.e., around $750 and $10 per MEG and EEG testing session, respectively). There are at least two reasons why ERFs might be preferred to ERPs. The first relates to the signal-to-noise ratio (SNR). At any given time in the brain, multiple sources (radial and tangential) are often simultaneously active. While MEG primarily picks

up activity from the sources that are tangentially oriented to the scalp, EEG picks up activity from deep sources, radial sources, and tangential sources (Hämäläinen et al., 1993; Luck, 2005a). While EEG signals are influenced by noise from radially oriented and deep sources, the tangential activity picked up by MEG is less influenced by noise due to selective cancellation of background brain noise (Ahlfors, Han, Belliveau, & Hämäläinen, 2010; Ahlfors et al., 2010, Goldenholz et al., 2009). The second reason ERFs are preferred relates to spatial resolution. While magnetic activity (measured by MEG) travels in a straight line through surfaces, electrical activity (measured by EEG) does not. Each time electrical activity hits a surface (i.e., of the brain, of the skull, of the scalp), it is distorted (Hämäläinen et al., 1993; Hari, Parkkonen, & Nangini, 2010; Luck, 2005a). Thus, in comparison to electrical activity, magnetic activity allows for more accurate estimations of where a brain response may be generated in the brain (i.e., its source). This in turn makes MEG superior to EEG for investigating hemispheric differences in processing, which are particularly important for studies of language and auditory processing (Johnson et al., 2013; Luck, 2005a, 2005b; Picton et al., 2000).

Studies of Auditory Processing in ASD using EEG and MEG

Due to its strengths in terms of spatial resolution and SNR, MEG might be the preferred tool used to study auditory processing. However, since EEG is a more established and widely-used than MEG, it is important to consider both MEG and EEG data regarding the processing of sounds in passive paradigms in individuals with ASD.

Obligatory ERP/ERFs

With regards to the early obligatory responses, the M50 to nonspeech sounds has been found to be atypical in latency (but not amplitude) in children with ASD (Oram Cardy, Flagg, Roberts, & Roberts, 2008), while the corresponding P1 ERP has been found to be diminished in children with ASD to both speech and nonspeech sounds (Lepistö et al., 2005) or to speech but not nonspeech sounds (Jansson-Verkasalo et al., 2003;

Whitehouse & Bishop, 2008). Similarly, the M100 to nonspeech stimuli has been found to be absent or delayed in latency in ASD, suggesting slower or incomplete maturation in these children (Gage, Siegel, & Roberts, 2003; Khan et al., 2010). The corresponding N1 ERP response has been found to be earlier (Ferri et al., 2003); later (Bruneau, Bonnet-Brilhault, Gomot, Adrien, & Barthélémy, 2003; Dunn, Vaughan Jr, Kreuzer, & Kurtzberg, 1999; Korpilahti et al., 2007; Seri, Cerquiglini, Pisani, & Curatolo, 1999); and smaller to nonspeech or speech sounds in children with ASD (Seri et al., 1999; Korpilahti et al., 2007). Further, the ERP N2 has been found to be smaller to nonspeech or speech sounds (Lepistö et al., 2005; Jansson-Verkasalo et al., 2003) or to speech but not nonspeech sounds (Whitehouse & Bishop, 2008).

Mismatch Negativity/Mismatch Field

Previous ERF studies have found that children with ASD have delayed or missing MMFs to nonspeech sounds (Roberts et al., 2010; Tecchio et al, 2003) or delayed MMFs to both speech and nonspeech sounds (Oram Cardy, Flagg, Roberts, & Roberts, 2005; Roberts et al., 2011). Previous ERP studies have found that children with ASD have MMNs to nonspeech sounds that are atypically large (Ferri et al., 2003); atypically small (Kuhl et al., 2005; Seri et al., 1999); unusually early (Ferri et al., 2003; Gomot, 2002; Martineau, Garreau, Barthelemy, & Lelord, 1984); or unusually late (Jansson-Verkasalo, et al., 2003; Seri et al., 1999). In contrast, two ERP studies have found that children with ASD have typical MMN responses to speech sounds for their age (Čeponienė et al., 2003; Kemner, et al., 1995). In terms of speech sounds, ERP studies have found that MMN responses are atypically large or small in children with ASD (Kujala et al., 2010), or are absent in pre-schoolers with ASD (Kuhl et al., 2005).

P300

Finally, with regards to the P300, studies have found children with ASD have atypical P300 responses to nonspeech sounds (Kemner et al., 1995; Lincoln, Courchesne,

Harms, & Allen, 1995); to speech sounds (Dunn, Vaughan Jr, Kreuzer, & Kurtzberg, 1999); to both speech and nonspeech sounds (Courchesne, Kilman, Galambos, & Lincoln, 1984); and to speech but not nonspeech sounds (Čeponienė et al., 2003; Lepistö et al., 2005).

In summary, MEG and EEG methods have the potential to provide important insights into the auditory processing abilities of individuals with ASD. However, the current findings present a mixed picture of the auditory processing deficits in these individuals. The studies in this thesis aimed to clarify the mixed findings by developing more reliable paradigms for measuring auditory processing for use in children with ASD. We review some of the reasons for the mixed findings in the Introduction of studies 1 and 3, and suggest a promising alternative for testing auditory discrimination in studies 3 and 4.

Outline of Studies in this Research Program

The studies presented in this thesis built on the existing body of work examining auditory ERPs and ERFs in individuals with autism and the relationship with language abilities. The following chapters are written as independent manuscripts according to the "thesis by publication" format. Thus, there is some overlap in content between manuscripts, particularly in the Introductions and Methods sections explaining the MEG system. All manuscripts were formatted in accordance to APA 6th Edition guidelines.

Study 1: The relationship between spoken language and speech and nonspeech processing in children with autism: an event-related field study

The initial aim of Study 1 was to look at the MMF to understand auditory discrimination to speech and nonspeech stimuli in children with ASD and its relationship with language impairment in ASD. However, we could not identify the MMN in almost half of the participants. In fact, despite its widespread use, there are many studies testifying to the poor reliability of the MMN and MMF, particularly when used to test children and

individuals with cognitive disorders (Badcock et al., 2013; Bishop, 2007; Kurtzberg, Vaughan Jr, Kreuzer, & Fliegler, 1995; Mahajan & McArthur, 2012; Uwer & von Suchodoletz, 2000). Thus, we focused instead on the robust obligatory brain responses elicited by repeated presentations of speech and nonspeech sounds. Using a within-subjects paradigm, combined with concurrent source and sensor MEG analyses, we found a strong association between the language skills of children with ASD and the extent to which their waveforms (for both speech and nonspeech sounds) resembled those of TD children at the level of the MEG sensors. From source analyses, we discovered that children's atypical brain responses to speech and nonspeech originated in the auditory cortex of the left hemisphere.

Study 2: Neuromagnetic responses to speech and nonspeech sounds in a minimally verbal child with ASD

Like most previous EEG and MEG studies of ASD, Study 1 involved a majority of high functioning children with ASD. However, an estimated 25-30% of people with ASD remain non-verbal/minimally verbal despite intervention (Anderson et al., 2007; Tager-Flusberg & Kasari, 2013). In Study 2, we had the opportunity to test one such child – an eight year old girl called GM who had never spoken – for her brain responses to speech and nonspeech sounds using MEG ERFs. GM showed a striking dissociation in her brain response to speech and nonspeech stimuli not seen in typically developing children or children with ASD who are with verbal ability. To test the reliability of this finding, we re-tested her two years later using a wireless gaming EEG system that children find more tolerable than MEG. The outcomes supported the MEG findings. Although preliminary, this case study demonstrates the potential of MEG and EEG for investigating cognition and brain function in this large but neglected subgroup of the autism spectrum.

Study 3: The magnetic acoustic change complex: a more robust and efficient neural measure of auditory discrimination?

Given our difficulties in eliciting a reliable MMF in Study 1, the aim of Study 3 was to develop a better alternative. The acoustic change complex (ACC; Martin and Boothroyd, 1999) is an ERP waveform consisting of a group of obligatory responses elicited by a change within an ongoing sound. It can be elicited by a variety of stimulus parameters, directly corresponds to behavioural tests of auditory processing, and is robust and reliable in adults and children. Given the possibilities of the ACC, we made a decision to forge a slightly different path for the remainder of the PhD, to enable us to ask the questions we set out to ask on auditory discrimination.

In Study 3, we recreated an optimal MMN paradigm for MEG, and developed a magnetic equivalent of the ACC (the mACC), which we tested on a group of normal hearing adults. We found that the mACC had a significantly greater SNR compared to the MMF elicited using the same stimulus changes. It was also more time-efficient. This suggests that the mACC may be more suitable as a test of auditory discrimination in child and clinical populations.

Study 4: Auditory discrimination and language impairment in children with autism spectrum disorders: a magnetic acoustic change complex (mACC) study

Study 4 brings us back full circle to our original questions : do children with ASD have poor auditory discrimination? Is this connected to their language ability, and if so how? To this end, we tested children with ASD and TD children on the mACC paradigm that we developed in Study 3. To our knowledge, this study is the first to apply the mACC (or the ACC) to ASD. We found that, on average, individuals with ASD had reduced mACCs, consistent with impairment in auditory discrimination. However, we found no reliable associations between mACC amplitude and spoken language ability at the individual level.

Summary

The overarching aim of this thesis is to better understand the relationship between auditory processing and language impairment in children with ASD. The existing evidence, at both the behavioural level and the neurological level, is decidedly mixed. In this research program, we attempted to clarify the relation between auditory processing and language in ASD by adopting or developing reliable MEG auditory measures. Specifically, in Study 1 (Chapter 2), we used passive auditory MEG ERFs at both the sensor and source level to measure auditory processing in children with ASD with varying degrees of language ability. In Study 2 (Chapter 3), we use the same MEG measures, plus a wireless EEG system, to compare the auditory processing of a nonverbal child with ASD to typically developing children as well as verbal children with ASD. In Study 3 (Chapter 4), we developed a new MEG measure of auditory discrimination (the mACC) with superior reliability and efficiency to the widely-used MMF. And in Study 4 (Chapter 5), we used the mACC to compare auditory discrimination in children with ASD and children with TD. In Chapter 6 (General Discussion), we summarise the outcomes of these experiments, and use them to outline the main theoretical and practical implications of this research program. We finish by discussing the limitations that we encountered in our studies, and how these limitations could be addressed by future research.

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Chapter 2

The relationship between spoken language and speech and nonspeech processing in children with autism: a magnetic event-related field study

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Abstract

It has been proposed that language impairments in children with Autism Spectrum Disorders (ASD) stem from atypical neural processing of speech and/or nonspeech sounds. However, the strength of this proposal is compromised by the unreliable outcomes of previous studies of speech and nonspeech processing in ASD. The aim of this study was to use a paradigm that maximised the reliability of outcomes to determine if there was an association between poor spoken language and atypical event-related field (ERF) responses to speech and nonspeech sounds in 14 children with ASD and 18 children with typical development. The results showed that poor spoken language scores were associated with atypical left-hemisphere brain responses (200 to 400 ms) to both speech and nonspeech in the ASD group. These data support the idea that some children with ASD may have an immature auditory cortex that affects their ability to process both speech and nonspeech sounds. Their poor speech processing may impair their ability to process the speech of other people, and hence reduce their ability to learn the phonology, syntax, and semantics of their native language.

Keywords: Autism Spectrum Disorder, language impairment, auditory processing, magnetic event-related fields

The Relationship Between Spoken Language and Speech and Nonspeech Processing in Children with Autism: An Event-related Field Study

Introduction

The language abilities of children with Autism Spectrum Disorders (ASD) vary widely, with children ranging from minimally verbal or mute (25-50%) to having typical language for their age (Boucher, 2003; Coleman, 2000; Jarrold, Boucher, & Russell, 1997; Kjelgaard & Tager-Flusberg, 2001; Klinger, Dawson, & Renner, 1996; Tager-Flusberg, 1981; Tager-Flusberg & Joseph, 2003; Tager-Flusberg & Kasari, 2013). A number of theories hold that poor spoken language in children with ASD stems from the atypical processing of sounds. For example, it has been proposed that children with ASD show an atypical bias away from social stimuli such as speech (Boddaert, 2004; Čeponienė et al., 2003; Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Dawson, 2004; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Klin, 2003); or are hyper- or hypo-aroused to both speech and nonspeech sounds (Järvinen-Pasley et al., 2008; Järvinen-Pasley & Heaton, 2007; Markram & Markram, 2010; Mottron, Dawson, Soulieres, Hubert, & Burack, 2006; Samson, Mottron, Jemel, Belin, & Ciocca, 2006); or have atypically acute processing of nonspeech sounds combined with impaired processing of speech sounds (Gervais et al., 2004; Kuhl, Coffey-Corina, Padden, & Dawson, 2005; Schreibman, Kohlenberg, & Britten, 1986).

Testing "auditory processing" theories in children with ASD at the behavioural level is often difficult due to limitations in their ability to understand task instructions, attend to long and repetitive tasks, or plan and execute responses (Allen & Courchesne, 2001; Roberts et al., 2008). To circumvent these problems, some researchers have used event-related fields (ERFs) or event-related potentials (ERPs) to measure speech and nonspeech processing in children with ASD without their attention (e.g., while they watched their favourite movie) or without having to make a complex response (e.g.,

counting sounds).

Auditory ERFs and ERPs represent the average pattern of magnetic (ERFs) or electrical (ERPs) activity elicited by groups of cells in the brain in response to sounds (Hari, Parkkonen, & Nangini, 2010; Luck, 2005). A mature "obligatory" auditory ERF response comprises M50, M100, M150, M200, and M300 responses (Näätänen & Picton, 1987). A mature obligatory auditory ERP response similarly comprises a P1 (similar to the M50), an N1 (similar to the M100), a P2 (similar to the M150), an N2 (similar to M200), and a P300 (similar to the M300; Hyde, 1997; Näätänen & Picton, 1987; Stapells, 2002).

It is important to note that auditory ERF and ERP responses of children differ to adults. The ERF responses of children have clear M50 (P1) and M200 (N2) peaks, but the size of their M100 varies considerably (Oram Cardy, Ferrari, Flagg, Roberts, & Roberts, 2004; Paetau, Ahonen, Salonen, & Sams, 1995; Ruhnau, Herrmann, Maess, & Schröger, 2011; Takeshita et al., 2002). Similarly, the ERP responses of children show a clear P1 and N2 response in early childhood, but their N1 and P2 peaks do not start to emerge until school-age, and only reach full maturity in adolescence (Čeponiene et al., 2005; Čeponienė, Torki, Alku, Koyama, & Townsend, 2008; Mahajan & McArthur, 2012; Pang & Taylor, 2000; Ponton et al., 2000).

Studies of auditory ERFs and ERPs in children with ASD have reported mixed findings. In ERF studies, the M50 to nonspeech sounds has been found to be atypical in latency (but not amplitude) in children with ASD (Oram Cardy, Flagg, Roberts, & Roberts, 2008). Similarly, the M100 to nonspeech stimuli has been found to be absent or delayed in latency in ASD, suggesting slower or incomplete maturation in these children (Gage, Siegel, & Roberts, 2003; Khan et al., 2010). In ERP studies, the P1 has been found to be atypical in children with ASD to both speech and nonspeech sounds (Lepistö et al., 2005; Jansson-Verkasalo et al., 2003) or to speech but not nonspeech sounds (Whitehouse & Bishop, 2008). The N1 has been found to be earlier (Ferri et al., 2003); later (Bruneau,

Bonnet-Brilhault, Gomot, Adrien, & Barthélémy, 2003; Dunn, Vaughan Jr, Kreuzer, & Kurtzberg, 1999; Seri, Cerquiglini, Pisani, & Curatolo, 1999; Korpilahti et al., 2007); and smaller to nonspeech or speech sounds in children with ASD (Seri et al., 1999; Korpilahti et al., 2007). The N2 has been found to be smaller to nonspeech or speech sounds (Lepistö et al., 2005; Jansson-Verkasalo et al., 2003) or to speech but not nonspeech sounds (Whitehouse & Bishop, 2008). Finally, studies have found children with ASD have atypical P3 responses to nonspeech sounds (Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1995; Lincoln, Courchesne, Harms, & Allen, 1993); to speech sounds (Dunn, Vaughan Jr, Kreuzer, & Kurtzberg, 1999); to both speech and nonspeech sounds (Courchesne, Kilman, Galambos, & Lincoln, 1984); and to speech but not nonspeech sounds (Čeponienė et al., 2003; Lepistö et al., 2005).

Another ERF and ERP response that has been used to measure speech and nonspeech processing in children with ASD is the mismatch field (MMF; the ERF version) or mismatch negativity (MMN; the ERP version). This is measured by comparing the size of an auditory brain response triggered by a frequently presented standard sound to a brain response triggered by a rarer deviant sound (Näätänen, Gaillard, & Mäntysalo, 1978). The size of the difference between the standard and deviant responses is thought to reflect the brain's ability to discriminate the deviant sounds from the standard sounds. Previous ERF studies have found that children with ASD have atypical or missing MMFs to nonspeech sounds (Roberts et al., 2010; Tecchio et al, 2003) or delayed MMFs to both speech and nonspeech sounds (Oram Cardy, Flagg, Roberts, & Roberts, 2005; Roberts et al., 2011). Previous ERP studies have been found that children with ASD have MMNs to nonspeech sounds that are atypically large (Ferri et al., 2003; Kujala et al., 2010; Lepistö et al., 2005); atypically small (Kuhl et al., 2005; Seri et al., 1999); unusually early (Ferri et al., 2003; Gomot, 2002; Martineau, Garreau, Barthelemy, & Lelord, 1984); or unusually late (Jansson-Verkasalo, et al., 2003; Seri et al., 1999). In contrast yet again, two studies have

found that children with ASD have typical MMN responses to speech sounds for their age (Čeponienė et al., 2003; Kemner, et al., 1995). In terms of nonspeech sounds, ERP studies have found that MMN responses are atypically large or small in children with ASD (Kujala et al., 2010), or are absent in pre-schoolers with ASD (Kuhl et al., 2005).

This brief summary of auditory ERF and ERP studies reveals a mix of evidence for atypical brain responses to speech and nonspeech sounds in children with ASD. These inconsistent findings might be explained by least five factors. One is the heterogeneous nature of ASD, which is diagnosed from a combination of impairments in social interaction, communication and language, and restrictive, repetitive and stereotyped behaviours and interests (APA, 2000). Not all children with ASD have the same combination of impairments, which means that not all children with ASD have poor spoken language (Coleman, 2000; Rapin & Dunn, 2003; Tager-Flusberg, 2004). Roberts et al. (2011) reported that children with ASD with concomitant language problems are more likely to show atypical brain responses to sounds. This suggestion predicts that only studies recruiting a large proportion of children with ASD with poor spoken language may find atypical auditory ERF or ERP responses in children with ASD.

A second factor is inconsistent testing paradigms (see Bomba & Pang, 2004; Haesen, Boets, & Wagemans, 2011; Kujala, Lepistö, & Näätänen, 2013; Seri, 2007 for reviews). Previous studies vary greatly in the type of speech or nonspeech processes measured (e.g., sensory detection, discrimination, prosody); the type of stimulus presented (e.g. environmental sounds, complex tones, natural voices); the type of auditory ERF or ERP measured (e.g., M50, M100, N1, P2, P3, MMN); and whether children are tested under passive conditions (e.g., children watch a DVD and ignore the sounds) or active conditions (e.g., children are asked to count target sounds). Unless the auditory processing deficit associated with ASD is extremely general, it is unlikely that every test paradigm will detect atypical brain responses to speech and nonspeech in children with ASD.

A third factor is the use of electrical brain responses (i.e., ERPs) by the majority of the studies. Electrical activity does not necessarily travel in a straight line. Instead, it is deflected or 'smeared' each time it hits a surface, such as the brain, the skull, or the scalp (Hari et al., 2010; Luck, 2005). The brains, skulls, and scalps of individuals vary considerably, which might affect the reliability of ERP data between subjects and between studies.

A fourth is the use of the MMF or MMN by some studies. The MMN is created by subtracting a robust ERF or ERP waveform to many standard sounds from a noisier ERF or ERP waveform to rarer deviant sounds (Picton et al., 2000; Picton & Taylor, 2007). The noisier waveforms for the deviant sounds make the MMN response less reliable than obligatory auditory ERPs (Badcock et al., 2013; McArthur, Bishop, & Proudfoot, 2003; Uwer & von Suchodoletz, 2000). This too could explain variability between study outcomes, particularly in children and clinical populations (Bishop, 2007).

A fifth factor is inappropriate measurement of developing auditory brain responses in children. As mentioned above, the auditory brain responses of young children do not include a mature M100, N1 or P2. The age at which these peaks start to emerge varies between children (Albrecht, Suchodoletz, & Uwer, 2000; Čeponiene et al, 2005; Pang & Taylor, 2000; Ponton et al., 2000; Sharma, Kraus, J. McGee, & Nicol, 1997). This variability makes traditional amplitude and latency measurements invalid, since these procedures return false values for missing peaks (Bishop & McArthur, 2004; McArthur & Bishop, 2005). False values produce unreliable outcomes, which could also explain why studies have produced inconsistent evidence for atypical brain responses to speech or nonspeech sounds in children with ASD.

In summation, a number of theories hold that poor spoken language in children with ASD stems from the atypical processing of speech and/or nonspeech sounds. ERF and ERP studies testing these hypothesises have produced inconsistent findings, which might

result from the aforementioned five factors that affect the reliability of auditory ERF and ERP outcomes. The aim of this study was to determine if children with ASD with poor spoken language have atypical brain responses to both speech and nonspeech sounds using a paradigm that maximised the reliability of the outcomes. Specifically, with regards to the heterogeneity of ASD, we examined the relationship between each individual's spoken language ability and auditory brain responses within the ASD and the typically developing (TD) groups separately, rather than averaging across heterogeneous groups. With regards to inconsistent testing paradigms, we measured obligatory auditory brain responses, which produce more robust and reliable waveforms than the MMN. Further, we used ERFs rather than ERPs since magnetic activity is not smeared by structures in the brain or head, and are less prone to noise (Hari et al., 2010). Finally, we measured auditory ERFs using a technique that produces valid data for missing peaks (i.e., the intra-class correlation (ICC); McArthur & Bishop, 2004). We predicted from the (albeit highly mixed) existing evidence that there would be a reliable relationship between spoken language ability and obligatory auditory ERFs to both nonspeech and speech sounds in the ASD group. This would support the hypothesis that children with ASD with poorer spoken language have less typical obligatory auditory ERFs to both nonspeech and speech sounds.

Methods

Written consent was obtained from parents of participants, and procedures were approved by the Macquarie University Human Research Ethics Committee.

Participants

All participants were aged between 6 and 14, spoke English as their first language at home and school, and had hearing in the normal range. Out of the 47 children recruited (24 ASD, 23 TD), 15 were excluded from the final sample. Reasons included behavioural difficulties and non-compliance during testing (three participants), not meeting group criterion for ASD or TD cut-offs (four participants), being unable to partake in the

behavioural tests because of minimal verbal skills (one participant), MEG trigger malfunction (two participants), and excessively noisy MEG data (five participants). This left us with 14 children with ASD and 18 children with TD in the final dataset.

Children with ASD were recruited from Autism Spectrum Australia, Macquarie University Special Education Centre, and the Autism Australasian research website. All were attending special education schools or "satellite classes" for children with ASD. Children whose parents could not provide a report from psychologists or paediatricians confirming ICD-10 or DSM-IV diagnoses of Autism were administered the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2002) to confirm a diagnosis of ASD. In addition, all children with ASD scored above the cut-off score of 15 on the Lifetime scale of the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003).

Children with TD were recruited through online advertisements to participate in a University-run school-holiday science program, and through friends and colleagues. To be included in the study, children had to be below the cut-off on the SCQ and have no known history of brain injury, hearing impairment, developmental disorders or Autism in their family.

As shown in Table 1, there were no significant differences between ASD and TD groups in terms of age ($t = -1.09$, $p > 0.05$), handedness ($t = 0.37$, $p > 0.05$), or gender ($t = 0.33$, $p > 0.05$). Both groups had normal auditory thresholds as tested with an Otovation Amplitude T3 series audiometer.

Table 1

Standardised Test Results for Children with Autism Spectrum Disorder (ASD) and Children with Typical Development (TD)

	ASD		TD		t- test	
	M (SD)	Range	*M (SD)*	Range	*t*	*p*
Age	10.82 (1.72)	6 - 14	10.02 (2.39)	7 - 13	1.05	0.30
Handedness	1.07 (0.27)	1 - 2	1.11 (0.32)	1 - 2	0.37	0.71
Gender	1.78 (0.43)	1 - 2	1.83 (0.38)	1 - 2	0.33	0.74
Matrices Test	8.71 (3.52)	4-14	12.44 (2.28)	9-16	3.44	<0.01
Peabody Picture Vocabulary Test	98.00 (23.96)	61-160	21.39 (15.39)	92-167	3.35	<0.01
Nonword Repetition Test	7.43 (1.99)	2-11	10.28 (1.67)	7-13	4.40	<0.01
Digit Span Test	6.57 (3.41)	1-13	10.61 (2.15)	7-15	4.10	<0.01
Recalling Sentences Test	5.71 (3.69)	1-11	10.72 (2.27)	7-15	4.47	<0.01
Test for Reception of Grammar	85.29 (18.49)	55-111	106.67 (8.94)	85-123	3.98	<0.01
Social Communication Questionnaire	24.57 (6.43)	17-37	2.33 (1.82)	0-6	12.56	<0.01

Note. Scores are standard or scaled scores with means and standard deviations of 100 and 15 or 10 and 3, respectively. Gender was coded 1 = female, and 2 = male. Handedness was coded 1 = right-handed, 2 = left-handed.

It is noteworthy that children with TD had a higher mean score than the ASD group for nonverbal IQ as measured by the Matrices subtest of the Wechsler Intelligence Scale

for Children (Wechsler, 2003; t = 3.44, p = 0.002). This difference was not a concern experimentally since we measured brain responses using a passive paradigm that did not require children to respond to, or learn, a task. Neither were they a concern statistically since we examined the association between brain responses to sounds and spoken language within groups, rather than between groups.

Standardised language tests

All participants were administered five language tests (see Table 1) to gauge their general spoken language ability. In the Peabody Picture Vocabulary Test items (PPVT-4 Form B; Dunn & Dunn, 2007), which indexed receptive vocabulary, children were asked to pick one out of four pictures that matched the spoken word. In the Test for Reception of Grammar items (TROG; Bishop, 2003), children were asked to choose one of four pictures that corresponded to a sentence read aloud by the examiner. In the Recalling Sentences subtest items (Clinical Evaluation of Language Fundamentals 4th Edition; Semel, Wiig, & Secord, 1987) - which indexes syntax, phonology, and semantics - children were asked to repeat 32 increasingly difficult sentences after the examiner. In the Nonword Repetition subtest items, which indexes short-term memory for phonemes, children were asked to repeat 18 increasingly difficult nonwords (Children's Test of Phonological Processing (CTOPP); Wagner, Torgesen, & Rashotte, 1999). Finally, in the Digit Span subtest (CTOPP), which tests short-term memory for digits, children were asked to repeat strings of numbers verbatim.

The TROG and PPVT have mean standard scores of 100 with a standard deviation (SD) of 15, while the remaining tests use mean scaled scores of 10 and a SD of 3. Standard and scaled scores were all converted to z-scores (M = 0 and SD = 1), which were averaged to create a spoken language composite score.

Auditory Stimuli

Each speech and nonspeech stimulus was 190 ms long (plus a 5-ms silence at the

start and end) and presented with a stimulus onset asynchrony (SOA) jittered between 900 and 1100 ms to avoid anticipatory brain responses. Stimuli were presented at 75 dB SPL via earphones attached to rubber air tubes (Model ER-30, Etymotic Research Inc., Elk Grove Village, IL).

The speech stimulus was a natural sounding English vowel /a/ created by McArthur, Atkinson, and Ellis (2009). An analogous nonspeech stimulus was created by combining three sine-wave tones of the same frequency as the first three formants of the speech sounds (see Figure 1 and Table 2). The speech sound contained an F0, and resembled an adult male voice, whereas the nonspeech did not contain an F0, and sounded like a complex tone. Most participants described the two sounds as being perceptually different, describing the speech sound as human speech, and the nonspeech sound as a robot or as a 'beep'.

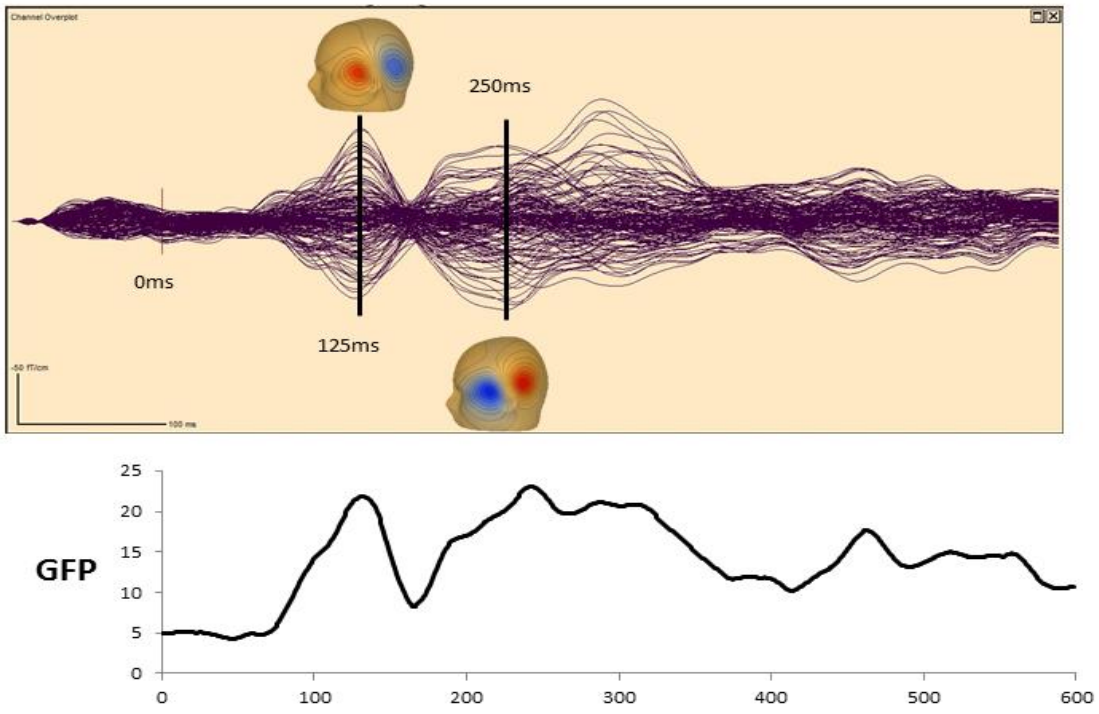

Figure 1. Example of an MEG butterfly plot (above) and its corresponding global field power (GFP) of averaged auditory responses (to a combination of speech and nonspeech)

from all 160 MEG sensors, from an 8-year-old typically-developing (TD) child. The marked peak times of 125 ms and 250 ms correspond to the EFR M50 (ERP N1) and ERF M150/M200 (ERP P2). The heads represent the source of activity from the TD child as estimated by the MEG sensors.

Table 2

Speech And Nonspeech Stimuli Acoustic Parameters

	Speech			Nonspeech		
Formant	Hertz	Milliseconds	Bandwidth	Hertz	Milliseconds	Bandwidth
F0	106-119	5-20	NA	NA	NA	NA
	120	25-80	NA	NA	NA	NA
	119-179	85-200	NA	NA	NA	NA
F1	700	5-200	70	700	5-200	NA
F2	1560	5-200	130	1560	5-200	NA
F3	2430	5-200	320	2430	5-200	NA

Children were presented with eight blocks of 100 speech stimuli interleaved with eight blocks of 100 nonspeech stimuli. The speech and nonspeech stimuli that are the focus of this study acted as frequent "standard stimuli" (85% of stimuli) presented amongst rare deviant sounds (15% of stimuli) within an oddball paradigm. We originally planned to use the standard and deviant stimuli to analyse the MMF (in addition to the obligatory ERFs) to speech and nonspeech sounds. However, like previous studies, we found the MMF far less reliable than obligatory ERFs to sounds (Mahajan et al., 2012; McArthur et al., 2003). Thus, this study focused solely on the obligatory ERFS to the standard speech and nonspeech stimuli.

Recording session

At the start of the recording session, an elasticised cap comprising five marker coils was placed on the participant's head, and the positions of the coils and the shape of the participant's head was measured with a pen digitiser (Polhemus Fastrack, Colchester, VT). Head position was measured with the marker coils before and after each recording. In addition, the children were visually monitored for head movements. Children who

exceeded head-movement of 5 mm (as pre-processed in MEG160) were excluded from further analyses. Marker coils were re-measured at the beginning and end of each stimulus block. During the recording, participants lay on a comfortable bed inside the magnetically shielded room and watched a silent subtitled DVD of their choice projected on the ceiling to keep them occupied and awake. They were told to ignore the sounds and give their full attention to the movie.

During the recording session, the data were recorded using 160 coaxial first-order gradiometers with a 50 mm baseline (Model PQ1160R-N2, KIT, Kanazawa, Japan; Kado et al. 1999; Uehara et al. 2008). Brain activity was bandpass filtered at .3 to 300 Hz and down-sampled at 1000 Hz.

Data processing

The recorded data was processed at two levels: at the MEG sensors and at the sources in auditory cortex. Although less common than source analyses, the sensor analyses are particularly important to this study for two reasons. First, unlike source analyses, sensor analyses do not depend on the fitting of dipoles, which is particularly difficult in children due incomplete knowledge about number and location of dipoles that should be fitted (Webb et al., 2013). Second, sensor analyses can act as an important "bridge" between ERP data reported in previous studies and ERF source outcomes. Specifically, ERF sensor activity is similar to ERP activity since it (1) requires no assumptions about the number of position of dipoles within the brain, and (2) is measured outside the brain. At the same time, ERF sensor activity can be highly correlated with fitted dipoles in terms of strength and latency (Kasai et al., 2002, 2003). It follows that if the ERF sensor outcomes of a study look similar to previous ERP outcomes, then it is likely that the ERF source data of that same study will be comparable to previous ERP outcomes (because the ERF source data is highly correlated with the ERF sensor data).

The initial stages of processing the sensor and source data were the same. First,

each child's continuous sensor recording was read into BESA 6.0 (MEGIS Software GmbH, Grafelfing, Germany) to allow co-registration of head measures and trigger values. The continuous sensor file was then filtered between 0.3 and 300 Hz; divided into 700-ms epochs that started 100 ms before the onset of a sound and ended 600 ms post-onset (i.e., -100 to 600 ms); and baseline corrected from -100 to 0 ms. Epochs with artefact greater than 5336fT/cm were excluded from further analyses. As mentioned at the start of 'Participants', five children were excluded from the analysis (ASD = 4, n TD = 1) because more than 25% of their epochs contained artefact. Thus, the final participant pool consisted of 18 children with TD and 14 children with ASD. Groups did not differ in the total number of accepted sensor epochs for speech sounds ($t = 0.39$, $p > 0.05$) or nonspeech sounds ($t = 0.21$, $p > 0.05$).

Sensor data. From this point onwards, the sensor and source data were processed differently. For the sensor data, the accepted speech and nonspeech epochs were averaged together to create speech and nonspeech sensor waveforms, which were imported into Microsoft Excel for GFP calculation. For each child, GFP was calculated by transforming data at each time point for each sensor waveform (N = 160) into absolute values. These absolute values were then averaged to produce separate GFP sensor waveforms to speech and nonspeech stimuli (see Figure 1 for an example of GFP sensor waveforms for speech and nonspeech). We then used intra-class correlations (ICCs) to measure how similar each child's own sensor waveform for nonspeech and speech stimuli was to the appropriate mean sensor waveform of controls in three different time windows: 65-165ms (incorporating the early auditory M50, M100, M150), 200-400ms (incorporating the M200 and P3), and 0-500 ms (including all these peaks). These time windows were based on the most prominent peaks within the grand mean. Similar to Bishop, Hardiman, Uwer, and Von Suchodoletz (2007a) and McArthur et al. (2009), we did not divide the TD group into age-bands because Bishop, Hardiman and Von Suchodoletz (2007b) found that the ICC

does not reveal developmental changes for the age-range and stimulus rates similar to those used in this study. Like McArthur et al. (2009), we did not remove each child from the averaged TD waveform. In line with Bishop and McArthur (2004; 2005), we applied Fisher-z transformations to ICC scores to improve linearity for parametric statistics. The lower a child's "speech ICC" or "nonspeech ICC", the less typical their sensor waveforms for their age.

We also used Fisher z ICCs to measure how similar each child's sensor waveform for speech was to their own sensor waveform for nonspeech (their "speech-nonspeech ICC"). An advantage of using this "within-subjects" ICC analysis is that children act as their own ideal matched control in terms of age, spoken language ability, non-verbal ability, degree of autism, and head size (i.e., the latter defining the distance between an individual's head and the MEG sensors). The lower a child's speech ICC, the less similar their sensor waveform to speech relative to their own response to nonspeech sounds.

Source data. We used the accepted speech and nonspeech epochs in the sensor data (see above) to determine accepted speech and nonspeech epochs for the source analysis. Using BESA 6.0, we combined accepted epochs for both speech and nonspeech stimuli to identify the focal point for localisation of auditory cortex activity (a maximum 1120 trials, with 560 trials of each condition). From the focal point of the combined speech and nonspeech condition, with a dipole fixed in the left hemisphere and in the right hemisphere, we extracted a speech and a nonspeech waveform for each of the hemispheres. We then fitted one dipole per hemisphere in a symmetrical fashion. Using principal components analysis (PCA), we identified each child's M50/M100 (equivalent to ERP P1-N1) in their dipole waveforms between 80 (±10ms) and 110 ms (±50ms). A period of 80-110ms was chosen to encompass the clearest obligatory peak in the group average. The extension of ±10ms and ±50ms (as above) was to allow for a more accurate source analysis of the latency delays for younger children or those with maturing waveforms (cf. Oram

Cardy et al., 2004). Additionally, the time window was adjusted systematically for each child to ensure that the identified waveform both originated from the auditory cortex and explained at least 85% of the variance. Using BESA, we optimised the dipole waveforms according to the orientation of the dipoles around each child's chosen M50/M100 (P1-N1) response (cf. Roberts et al., 2010; 2011).

The left and right hemisphere source waveforms measured at each dipole for speech and nonspeech were exported into Excel (see Figure 2 for grand averages of the left and right hemisphere responses of both groups). In line with the sensor analysis, we planned to use ICCs to measure how similar each child's own waveform for nonspeech and speech stimuli was to the appropriate mean waveform of controls in three different time periods (65-165 ms, 200-400 ms, and 0-500 ms). However, in the source analysis, we struck an intractable problem. As outlined above, we used PCA to identify each child's M50/M100 between 80 (±10 ms) and 110 ms (±50 ms) and then 'optimised' the orientation of the dipoles to provide the best fit to the data. The difficulty we encountered was that it is entirely arbitrary which direction along the dipole is positive and which is negative. With adult data, it is relatively straightforward to invert any dipoles so that all participants have consistent waveforms (e.g., setting the M50 to always be positive and the M100 negative). Unfortunately, with child data, due to the variability in both the timing and the amplitude of the M50 and M100 response, it is often difficult to determine whether the source waveform should be inverted. For example, a large deflection at 90 ms could signal a late and immature M50 response or an early and mature M100 response. Thus, we could not average across TD participants, nor could we compare each individual's own speech or nonspeech dipole waveform to the mean waveform of the TD group. However, like the sensor analysis, we were able to calculate Fisher z ICCs to index the similarity of each child's nonspeech and speech dipole waveforms (i.e., their speech-nonspeech ICC) because each child's speech and nonspeech source waveform was optimised in exactly the

same way for both conditions. As per the source analysis, the lower a child's speech-nonspeech ICC, the less typical their source waveform to speech relative to their source waveform to nonspeech sounds.

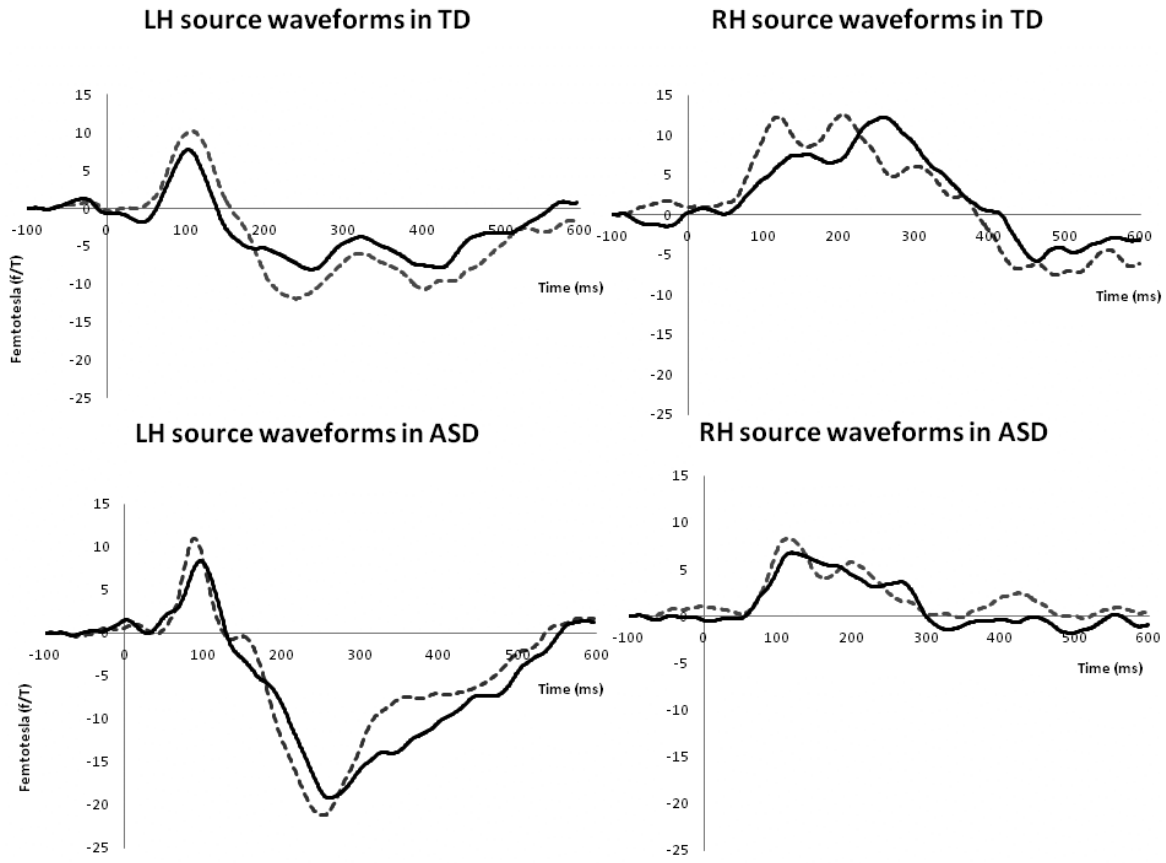

*Figure 2***.** Grand-average source waveforms from dipole fitting for speech (bold line) and nonspeech sounds (dotted grey line) in children with Autism Spectrum Disorder (ASD) and typically developing (TD) children in the left hemisphere (LH) and right hemisphere (RH*).*

Results

Sensor waveforms

This study predicted that less typical brain responses to speech and nonspeech sounds would be associated with poorer spoken language scores in the ASD group. Since

not all children with ASD have spoken language deficits, we did not expect all children with ASD to have poor ICCs for nonspeech and speech sounds. Thus, we did not necessarily expect a significant difference between the mean ICCs of the ASD and TD groups. Nevertheless, for the sake of completeness, we used independent-samples t-tests to compare the mean speech ICCs, nonspeech ICCs, and speech-nonspeech ICCs of the ASD and TD groups in the 65-165 ms, 200-400 ms, and 0-500 ms time periods of the sensor waveforms (see Table 3). As we expected, the mean ICCs of the ASD group did not differ significantly from the TD group, although the mean ICCs of the ASD group tended to be lower than the TD group. This suggested that a subgroup of children with ASD did have lower ICC scores than children with TD.

To directly test our prediction that atypical brain responses to speech and nonspeech sounds would be associated with poor spoken language scores in the ASD group, we calculated Pearson r correlation coefficients between language composite scores and nonspeech ICCs, speech ICCs, and speech-nonspeech ICCs in the 65-165 ms, 200-400 ms, and 0-500 ms time periods of the sensor waveforms for the ASD and TD groups separately (see Table 4 and Figure 3). In line with Cohen (1988), we considered r values of 0.1, 0.3, and 0.5 to be small, moderate, and large (respectively) in effect size.

Table 3

Mean (M) and standard deviation (SD); Speech Intraclass Correlations (ICCs), Nonspeech ICCs, And Speech-Nonspeech ICCs for Children with Autism Spectrum Disorder (ASD) and Children with Typical Development (TD) for Sensor and Source (Left and Right Hemisphere) Waveforms in the 65-165 ms, 200-400 ms, and 0-500 Ms Time Windows

	ASD (N = 14)		TD (N = 18)		t-test	
	M (SD)	Range	*M (SD)*	Range	*t*	*p*
Sensor speech ICCs						
0-500 ms	0.74 (0.64)	-0.74-1.65	0.85 (0.48)	-0.21-1.57	0.55	0.59
65-165 ms	0.27 (0.65)	-1.27-1.57	0.43 (0.52)	-0.48-1.58	0.78	0.44
200-400 ms	-0.02 (0.78)	-1.75-0.93	0.00 (0.65)	-1.25-1.08	0.07	0.94
Sensor nonpseech ICCs						
0-500 ms	0.63 (0.44)	-0.17-1.39	0.94 (0.49)	0.02-1.72	1.84	0.08
65-165 ms	0.47 (0.43)	-0.27-1.41	0.45 (0.53)	-0.64-1.75	-0.09	0.93
200-400 ms	0.21 (0.65)	-0.92-1.56	0.51 (0.73)	-0.70-2.17	1.21	0.24
Sensor speech-nonspeech ICCs						
0-500 ms	0.98 (0.56)	-0.44-1.64	1.11 (0.40)	0.35-1.77	0.76	0.45
65-165 ms	0.58 (0.36)	-0.16-1.47	0.73 (0.49)	-0.26-1.47	0.91	0.37
200-400 ms	0.65 (0.65)	-1.08-1.56	0.41 (0.49)	-0.45-1.11	-1.16	0.25
Source speech-nonspeech ICCs (LH)						
0-500 ms	1.11 (0.58)	-0.34-1.89	1.09 (0.47)	-0.05-1.99	-0.10	0.92
65-165 ms	0.70 (0.52)	-0.35-1.41	0.45 (0.53)	-0.72-1.33	-1.28	0.21
200-400 ms	1.04 (0.52)	-0.3-1.76	0.99 (0.51)	-0.04-2.01	-0.27	0.79
Source speech-nonspeech ICCs (RH)						
0-500 ms	1.03 (0.37)	0.37-1.69	1.27 (0.40)	0.68-2.35	1.68	0.10
65-165 ms	0.55 (0.52)	-0.66-1.28	0.53 (0.65)	-0.52-1.66	-0.03	0.97
200-400 ms	0.92 (0.38)	0.31-1.51	1.14 (0.46)	0.65-2.37	1.46	0.15

Within the TD group, composite language scores were not significantly correlated to any ICC measure (see Figure 4). In contrast, in the ASD group, language composite scores were significantly and strongly correlated to speech ICCs at 0-500 ms ($r = 0.67$, $p < 0.01$), speech ICCs at 200-400 ms ($r = 0.74$, $p < 0.01$), nonspeech ICCs at 0-500 ms ($r = 0.70$, $p < 0.01$), and nonspeech-speech ICCs at 0-500 ms ($r = 0.53$, $p = 0.05$). In addition, nonspeech ICCs and speech ICCs were strongly correlated in the ASD group (0-500 ms: $r = 0.98$, $p < .0.01$; see Figure 5). This, paired with the significant and strong correlations between language composite scores and speech-nonspeech ICCs, suggested that poorer language composite scores were associated with less typical brain responses for both speech and nonspeech sounds in the ASD group.

Table 4

*Pearson r Correlation Coefficients for Typically Developing (TD) and Autism Spectrum Disorder (ASD) Groups Calculated Between Language Composite Scores and Speech Intraclass Correlations (ICCs), Nonspeech ICCs, And Speech-Nonspeech ICCs for Sensor and Source (Left and Right Hemisphere) Waveforms in the 65-165 ms, 200-400 ms, and 0-500 ms Time Windows. Statistically Significant Relationships are Marked with **

	TD			ASD		
Time period (ms)	0-500	65-165	200-400	0-500	65-165	200-400
Sensor waveforms						
Speech ICCs	0.12	0.19	-0.08	0.67*	0.34	0.74*
Nonspeech ICCs	0.08	-0.01	0.02	0.70*	-0.08	0.62
Speech-nonspeech ICCs	0.12	-0.26	-0.14	0.53*	-0.02	0.45
Source waveforms (LH)						
Speech-nonspeech ICCs	0.48*	-0.08	0.34	0.67*	0.27	0.67*
Source waveforms (RH)						
Speech-nonspeech ICCs	0.04	-0.05	-0.10	0.30	0.36	0.27

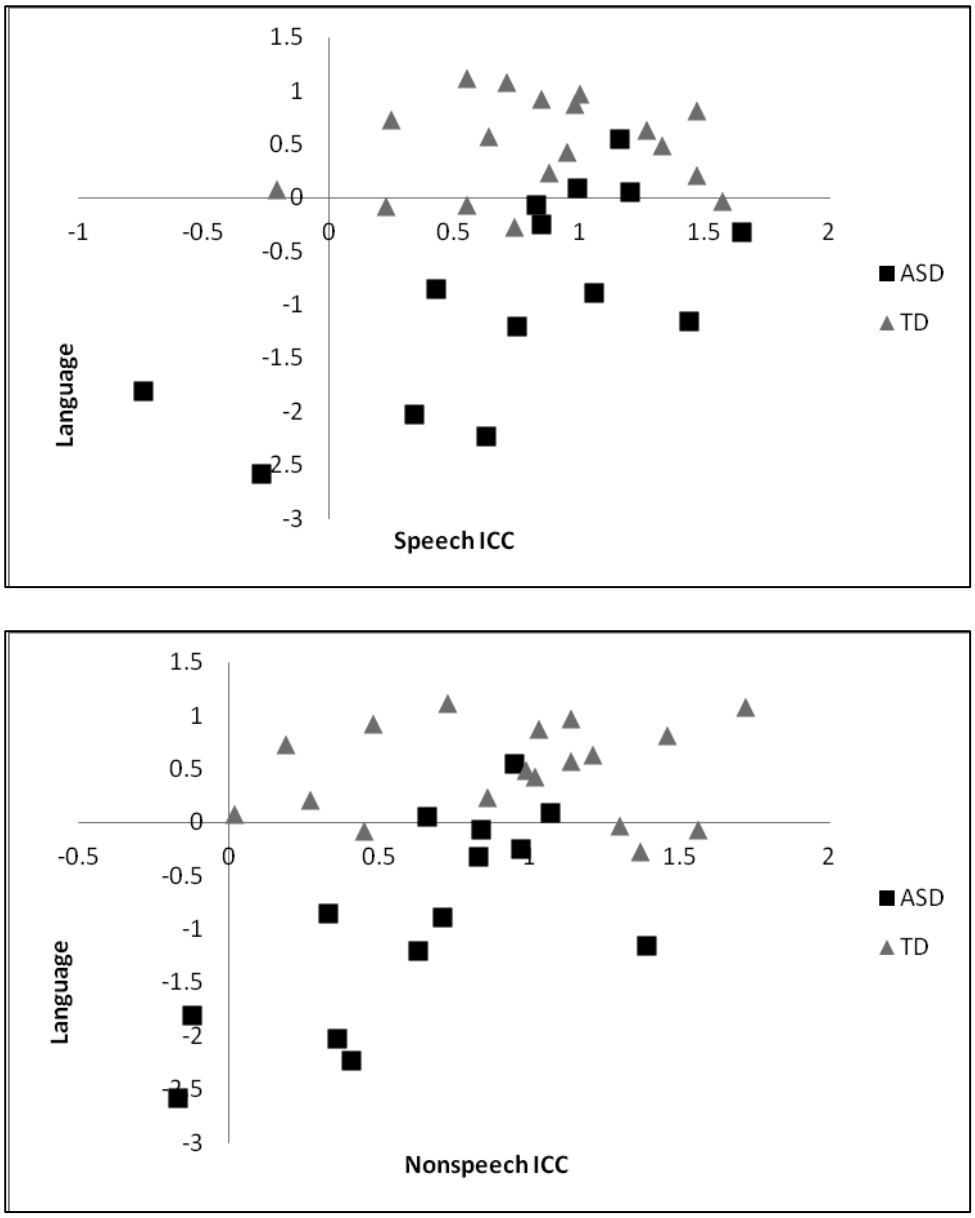

Figure 3. Language composite scores plotted against speech intra-class correlation coefficients (ICC) and nonspeech ICCs for sensor waveforms across the 0-500 ms time window for children with typical development (TD; triangles) and Autism Spectrum Disorder (ASD; squares).

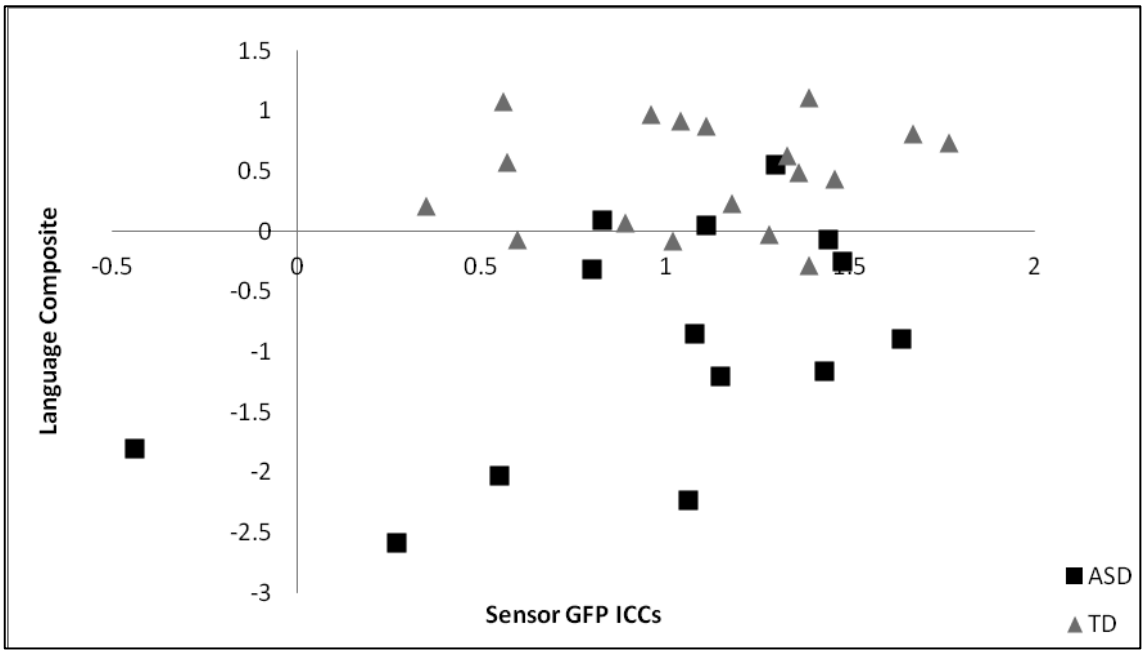

Figure 4. Language composite scores plotted against speech-nonspeech intra-class correlation coefficients (ICC) for sensor waveforms across the 0-500 ms time window for children with typical development (TD; triangles) and Autism Spectrum Disorder (ASD; squares).

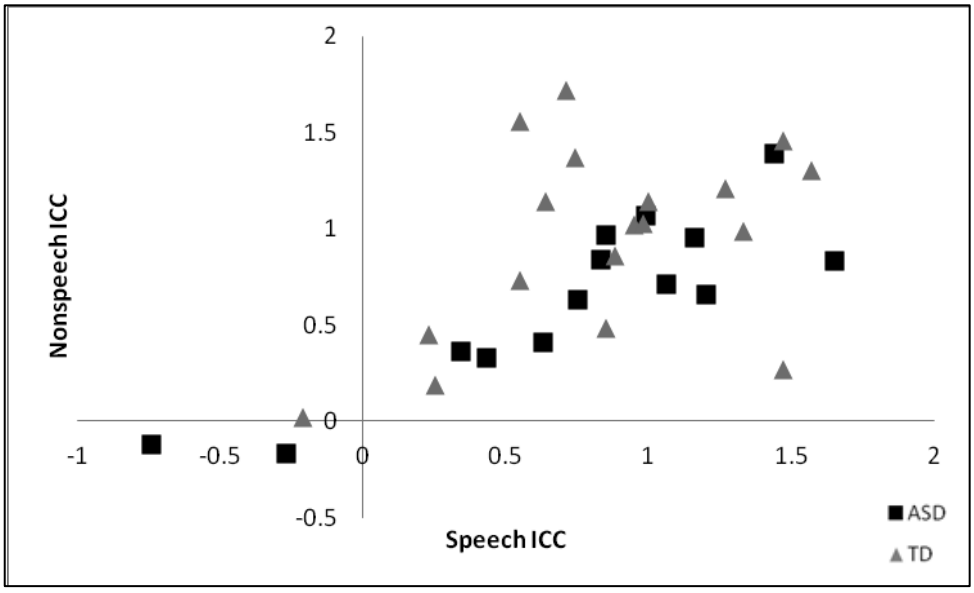

Figure 5. Speech intra-class correlation coefficients (ICC) plotted against nonspeech ICCs for sensor waveforms across the 0-500 ms time window for children with typical development (TD; triangles) and Autism Spectrum Disorder (ASD; squares).

To ensure the relationships between language composite scores and ICC scores in the ASD group could not be explained by a third 'general' factor that correlated with both language and ICC scores, we calculated Pearson r correlation coefficients within the ASD group between nonverbal IQ, age, language composite scores, speech ICCs (0-500 ms and 200-400 ms), nonspeech ICCs (0-500 ms) and nonspeech-speech ICCs (0-500 ms). Age was not significantly correlated with language composite scores (r = 0.03) or any ICC scores (r = -0.21 to -0.43; p > 0.05). Nonverbal IQ was significantly correlated with language composite scores (r = 0.76, p < 0.01), but not any ICC scores (r = 0.41-0.52; p > 0.05).

Despite the fact that language composite scores and ICC scores in the ASD group were not concurrently (significantly) correlated with nonverbal IQ and age, some of the associations were moderate-to-strong in size. Thus, to err on the side of caution, we calculated partial correlations between language composite scores and ICC scores in the ASD group controlling for age (speech ICC 0-500 ms: r = 0.74, p < 0.01; speech ICC 200-400 ms: r = 0.84, p < 0.01; nonspeech ICC 0-500 ms: r = 0.77, p < 0.01; nonspeech-speech ICC 0-500 ms: r = 0.55, p = 0.05) and nonverbal IQ (speech ICC 0-500 ms: r = 0.50, p = 0.08; speech ICC 200-400 ms: r = 0.63, p = 0.02; nonspeech ICC 0-500 ms: r = 0.65, p = 0.02; nonspeech-speech ICC 0-500 ms: r = 0.36, p = 0.22). The effect sizes were slightly enhanced when controlling for age, and slightly reduced when controlling for nonverbal IQ. Thus, the Pearson r correlations between language and ICC scores in the ASD group did not appear to be explained by age or non-verbal IQ. Thus, the sensor waveforms supported the prediction that children with ASD with poor spoken language have atypical brain responses to both nonspeech and speech sounds.

Source waveforms

We analysed the source data in the same way as the sensor data, with the exclusion of the speech ICCs and nonspeech ICCs, which we could not calculate due to problems

with optimising the source waveforms for dipole fitting (see Source Data section above under Methods). Table 3 shows the mean (with SD) speech-nonspeech ICCs for the ASD and TD groups for the 65-165 ms, 200-400 ms, and 0-500 ms regions for the sensor waveforms in the left and right hemispheres. Similar to the sensor waveforms, independent-samples t-tests revealed no statistically significant difference between the speech-nonspeech ICC scores of the TD and ASD groups in any time period in either hemisphere.

Figure 6 shows the associations between language composite scores and speech-nonspeech ICCs in each hemisphere for ASD and TD groups separately, further broken down into the 65-165 ms, 200-400 ms, and 0-500 ms time periods in Table 4. In the TD group, language composite scores were significantly associated with speech-nonspeech ICCs during 0-500 ms in the left hemisphere ($r = 0.48$, $p = 0.04$). Within the ASD group, language composite scores were significantly and strongly associated with left hemisphere speech-nonspeech ICCs from 0-500 ms ($r = 0.67$, $p < 0.01$) and 200-400 ms ($r = 0.67$, $p < 0.01$; Note: the same values are not an error). As can be seen in Table 4 and Figure 6, there was no association between language composite scores and speech-nonspeech ICCs in the right hemisphere in either group.

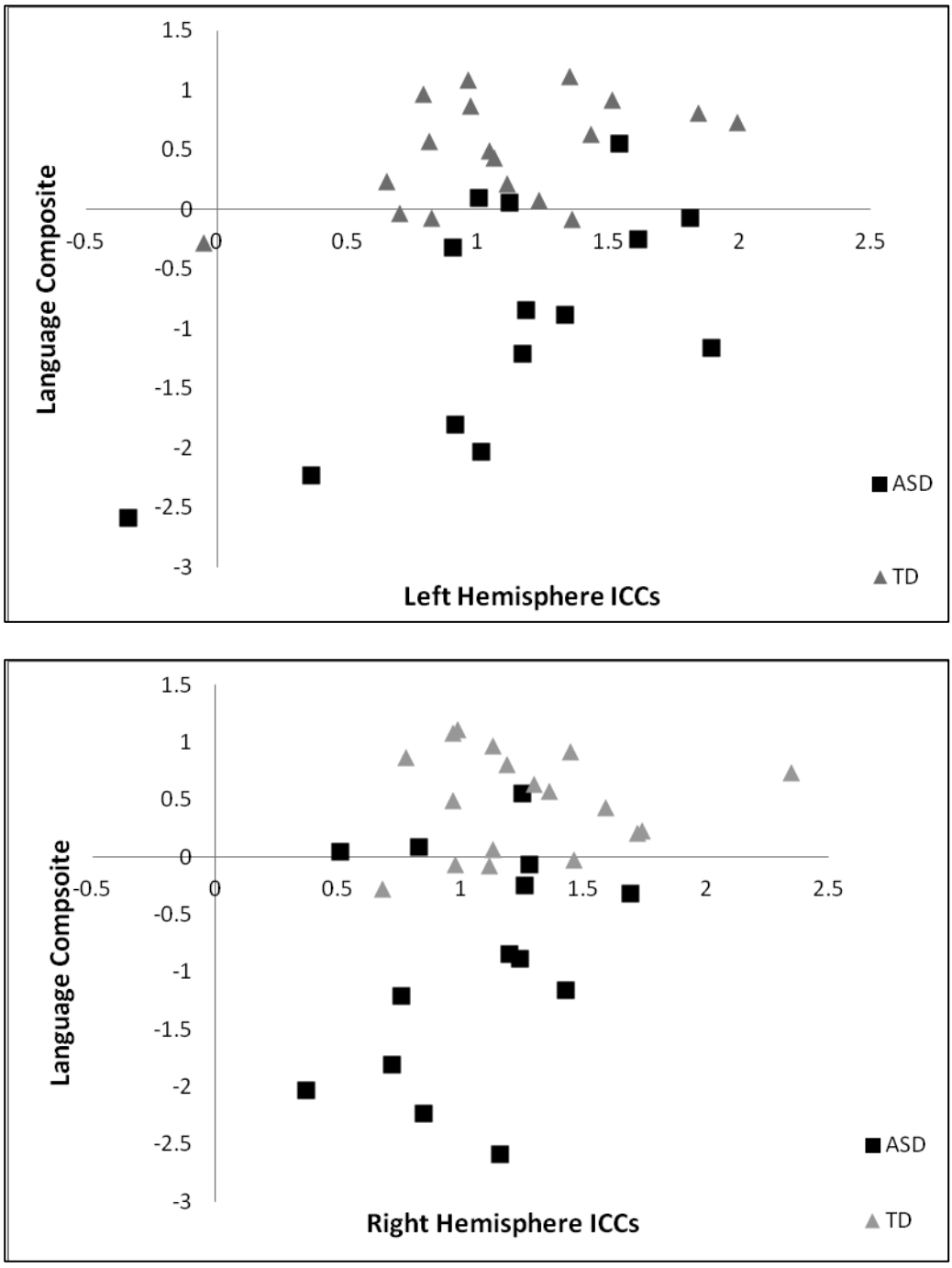

Figure 6. Language composite scores plotted against speech-nonspeech intra-class correlation coefficients (ICC) for left- and right-hemisphere source waveforms across the 0-500 ms time window for children with typical development (TD; triangles) and Autism Spectrum Disorder (ASD; squares).

We again examined the data to determine if the associations between language and ICC scores within the ASD group could be explained by a third general factor (i.e., age or nonverbal IQ). As outlined above, age was not significantly correlated with language composite scores ($r = 0.03$, $p < 0.05$). In addition, it was not significantly correlated to left hemisphere speech-nonspeech ICC scores (0-500 ms: -0.24; 200-400 ms: -0.13; $p > 0.05$). Again, as outlined above, nonverbal IQ was significantly correlated with language composite scores ($r = 0.76$, $p < 0.01$). However, it was not significantly correlated with left hemisphere speech-nonspeech ICC scores (0-500 ms: $r = -0.42$; 200-400 ms: $r = -0.44$; $p > 0.05$).

Although, yet again, age and nonverbal IQ were not significantly correlated with both language composite and ICC scores, we calculated partial correlations between language composite scores and left-hemisphere ICCs scores in the ASD group controlling for age (speech-nonspeech ICC 0-500 ms: $r = 0.54$, $p = 0.02$; speech-nonspeech ICC 200-400 ms: $r = 0.37$, $p = 0.14$) and for nonverbal IQ (speech-nonspeech ICC 0-500 ms: $r = 0.58$, $p = 0.04$; speech-nonspeech ICC 200-400 ms: $r = 0.57$, $p = 0.04$). The effects were slightly reduced when controlling for age and nonverbal IQ, but all bar the non-speech ICC at 200-400 remained strong and statistically significant. Thus, the Pearson r correlations between language composite and sensor speech-nonspeech ICCs scores in the ASD group appeared to be valid.

Since both the sensor and source data revealed significant associations between language composite scores and speech-nonspeech ICCs in the ASD group, and since the source data clearly suggested that less typical brain responses to both speech and nonspeech sounds were related to poorer language composite scores, the poor speech-nonspeech ICCs at the sensor level appeared to support the hypothesis that children with ASD with poor spoken language have atypical processing for both speech and nonspeech sounds. Further, the source data suggested that this deficit was located in the left

hemisphere. This left hemisphere deficit appeared to reflect processes in the 200-400ms range, since the whole waveform (0-500 ms) that contained the 65-165 ms window, as well as the 200-40 ms window, was correlated with spoken language, while the 65-165ms window was not.

Discussion

The aim of this study was to determine if children with ASD with poor spoken language had atypical brain responses to speech and nonspeech using a paradigm that maximised the reliability of outcomes. To this end, we indexed the speech and nonspeech ERFS of 14 children with ASD and 18 children with TD. Using both sensor and source data, we calculated Pearson r correlation coefficients between language composite scores and nonspeech ICCs, speech ICCs, and speech-nonspeech ICCs in the 65-165 ms, 200-400 ms, and 0-500 ms time periods for the ASD and TD groups separately. Below we use the outcomes of the sensor and source analyses to discuss the primary outcomes of this study. We then address the limitations of this study, which point to new directions for research on the relationship between speech and nonspeech processing and spoken language in ASD.

Primary outcomes

The primary prediction of this study was that atypical brain responses to speech and nonspeech sounds would be associated with poor spoken language scores in the ASD group. This prediction was supported by the sensor and source analysis. Pearson r correlations between nonspeech ICCs, speech ICCs, and speech-nonspeech ICCs at the sensor level revealed that language composite scores were strongly and significantly correlated to speech ICCs at 0-500 ms, speech ICCs at 200-400 ms, nonspeech ICCs at 0-500 ms, and speech-nonspeech ICCs at 0-500 ms in the ASD. In addition, nonspeech ICCs and speech ICCs were strongly correlated in the ASD group. These outcomes were backed by the source data, which revealed that language composite scores in the ASD group were significantly and strongly associated with left hemisphere speech-nonspeech ICCs from 0-

500 ms and 200-400 ms. Considered together, these findings suggest that children with ASD with poorer language composite scores have less typical processing between 200 and 400 ms in their left hemisphere that affects their ability to process sounds in general, since it affects their brain responses to both speech and nonspeech sounds.

As outlined in the Introduction, there are three main theories accounting for an association between poor spoken language and atypical speech or nonspeech processing: (1) children with ASD have an atypical bias away from social stimuli such as speech; (2) children with ASD are hyper- or hypo-aroused to both speech and nonspeech sounds; and (3) children with ASD have atypically acute processing of nonspeech sounds but poor discrimination of speech sounds. The findings of the present study do not support the first hypothesis, since children with ASD with poor spoken language did not have atypical brain responses to speech sounds alone. Neither do they support the third theory, since one would predict that brain responses responsible for atypically acute processing of nonspeech sounds would differ considerably from brain responses responsible for poor processing of speech sounds. This would lead to low ICCs between individual's MEG responses to speech and nonspeech sounds at both the sensor and source level. Yet in this study, these ICCs were strong.

This leaves us with the second hypothesis that children with ASD are hyper- or hypo-aroused to both nonspeech and speech sounds. One might predict that hyper- and hypo-arousal to sounds would lead to larger and smaller brain responses, respectively. An examination of the MEG source waveforms in Figure 2 shows that children with ASD, as a group, have much larger left-hemisphere MEG speech and nonspeech responses in the 200-400 ms time period than children with TD. At first glance, this might be taken as evidence for hyper-arousal to speech and nonspeech sounds in children with ASD. However, an equally plausible explanation is that children with ASD simply have immature brain responses to speech and nonspeech sounds for their age. Previous studies

have established that young children have larger M50/P1 and M150/M200/N2 responses than older children (Čeponienė et al., 2005; Čeponienė et al., 2008; Mahajan & McArthur, 2012; Oram Cardy et al., 2004; Paetau et al., 1995; Pang & Taylor, 2000; Ponton et al., 2000; Ruhnau et al., 2011; Takeshita et al., 2002). There is also evidence that such immaturities explain atypical brain responses to speech and nonspeech sounds in children with specific language impairment (Bishop et al., 2007a; Bishop & McArthur, 2004; Bishop & McArthur 2005). The large peaks in the ERF waveforms of the ASD group in this study (see Figure 2) look remarkably similar to immature P1 and N2 ERPs. Thus, children with ASD with poor spoken language may have immature brain responses to speech and nonspeech sounds.

The idea that children with ASD may have delayed or abnormal maturation of the auditory cortex has been suggested in previous ERP (Courchesne et al., 1984; Korpilahti et al., 2007; Kujala et al., 2010; Lepistö et al., 2005; Lepistö et al., 2006) and ERF studies (Gage et al., 2003; Khan et al., 2010; Oram Cardy et al., 2004; Roberts et al., 2011; Roberts et al., 2010). Of particular relevance is a study by Khan et al. (2010), which not only found that children with ASD had less mature auditory waveforms (i.e., a higher occurrence of M50, and a lack of bilateral M100), but that these immature waveforms were more prevalent in children with ASD with comorbid language impairment.

How might immature speech or nonspeech sounds give rise to higher-level spoken language problems? In this study, we found that the association between poor spoken language ability and atypical auditory brain responses to sounds appeared to stem from impaired processing in the left hemisphere between 200 to 400 ms. In ERPs, this part of the auditory brain response includes (1) the P300 (also called the P3), which is thought to reflect the meaningfulness, relevance, and probability of stimuli (see Picton, 1992 for a review); (2) the frontal N300, which is thought to play a role in early emotional evaluation of stimuli (Paulmann & Kotz, 2008a, 2008b); and (3) the N4, which has been found to be

sensitive to the 'speechness' of a sound (Čeponienė et al., 2005; Čeponienė et al., 2008). Because our speech and nonspeech stimuli were matched in terms of relevance and probability, and because children had similar brain responses to sounds regardless of "speechness", it seems more likely that the atypical brain responses of children with ASD with poor spoken language may relate to the meaningfulness or emotional valuation of the stimuli. If this is true, then children with ASD with poor spoken language may have an immature auditory processing system that fails to recognise the greater meaning of speech stimuli over nonspeech stimuli. This may inhibit the natural tendency to attend to speech stimuli rather than nonspeech stimuli (Vouloumanos & Werker, 2007), which may impede the rate at which a child learns the phonology, syntax, and semantics of their native language. Whilst highly speculative at this stage, the fact that this hypothesis explains all the major findings of this study suggests that it may deserve scrutiny by future research.

Limitations

This study is the first to examine the relationship between the spoken language abilities of children with ASD and their auditory ERFs in waveforms measured at both the sensors and the source. Given the limited and contradictory findings upon which this study was designed, it is perhaps inevitable that it had a number of limitations. One was the failure to calculate speech ICCs and nonspeech ICCs for the source data because we were unable to create an average source waveform for the TD group. As outlined above, this occurred because the source waveforms for each child were optimised to the most prominent peak in their individual waveforms, creating a unique pattern of waveforms per child that depended on the maturity of their waveforms. Ideally, we could have generated average waveforms for each age (e.g. 6, 7, 8, 9, 10, 11, 12, 13, 14). However, our TD sample size of 18 was too small for this to be viable. Ours is not the first study to encounter issues with source localisation in children (Pang, 2003, 2011; Webb et al., 2013). Future studies might avoid some of these problems by using definitive methods of

source analysis accounting for all generators involved in the auditory response, the interaction of multiple sources, and the use of paediatric head models for source analysis. Whenever possible, this should be supported by structural MRI scans or continuous head position monitoring, and a sample of children that is age-matched and categorised according to clear age cut-offs. Alternatively, studies could use an approach similar to ours that measures ERFs at sensors as well as sources. Sensor activity is highly correlated with MEG source activity and so has been said to be a good substitute for missing source data (Kasai et al., 2002, 2003).

A second limitation of the current study is the modest number of children in the ASD group (N = 14) despite initially screening of 24 children with ASD. Small samples compromise the power of a study to detect significant effects. In this study, this was not a particular problem since the effects within the ASD group were strong enough to be detected even in a modest sample size; and since the strong relationships between variables in the ASD group were representative of the entire group, and were not driven by a few outliers (see figures 3 to 5). Nevertheless, future studies would do well to recruit a larger number of children for the ASD sample.

Another potential limitation of this study was the similarity of our speech and nonspeech stimuli. It was important to match the acoustics of the speech and nonspeech stimuli as much as possible to aid interpretation of the outcomes. Specifically, if we had found an association between spoken language and brain responses to speech but not nonspeech, we needed to be as sure as possible that this stemmed from differences in the "nature" of the sounds (i.e., speech versus nonspeech) rather than differences in the acoustics of the sounds (i.e., frequency, amplitude, transitions). As outlined in the Methods, when asked, children described the speech sounds as human speech, and the nonspeech sounds as "beeps", which suggests that the speech and nonspeech sounds were perceive appropriately despite their close acoustic match. Nevertheless, future studies

might consider adding a third condition that measures brain responses to natural speech to ensure these produce the same waveforms as acoustically modified speech sounds.

Summary

This study tested the association between poor spoken language and poor speech and nonspeech processing in ASD using a paradigm that aimed to maximise the reliability of the outcomes. The primary finding was that children with ASD with poorer language composite scores had impaired processing between 200 and 400 ms in the left hemisphere, which appeared to affect the processing of both speech and nonspeech sounds. Combined with the outcomes of previous studies, this outcome suggests that children with ASD with poor spoken language may have an immature auditory processing system that fails to recognise the meaningfulness of speech over nonspeech sounds. This may limit a natural bias to attend to speech over nonspeech sounds, and hence impede the rate at which a child learns the phonology, syntax, and semantics of their native language.

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Chapter 3

Case report: Auditory brain responses in a nonverbal child with autism spectrum disorder and cerebral palsy

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Abstract

An estimated 30% of individuals with autism spectrum disorders (ASD) remain minimally verbal into late childhood, but research on cognition and brain function in ASD focuses almost exclusively on those with good or only moderately impaired language. Here we present a case study investigating auditory processing of GM, a nonverbal child with ASD and cerebral palsy. At the age of 8 years, GM was tested using magnetoencephalography (MEG) whilst passively listening to speech and nonspeech sounds. Where typically developing children and verbal autistic children all demonstrated similar brain responses to speech and nonspeech sounds, GM produced much stronger responses to nonspeech than speech, particularly in the 65 – 165 ms (M50/M100) time window post stimulus onset. GM was retested aged 10 years using electroencephalography (EEG). Consistent with her MEG results, she showed an unusually early and strong response to pure tone stimuli. These results demonstrate both the potential and the feasibility of using MEG and EEG in the study of minimally verbal children with ASD.

Keywords: Autism, language impairment, magnetoencephalography, event-related potentials, auditory processing, cerebral palsy

Brain Responses to Speech and Nonspeech Sounds in a Nonverbal Child with Autism Spectrum Disorder (ASD) and Cerebral Palsy

Introduction

According to recent estimates, around 30% of individuals with autism spectrum disorders (ASD) remain nonverbal or minimally verbal despite intervention (Coleman, 2000; Mody & Belliveau, 2013; Tager-Flusberg & Kasari, 2013). A significant proportion of these individuals never speak, while others remain at the stage of echolalia or have a limited repertoire of fixed words and phrases either spoken or communicated through alternative/augmentative communication systems (Kasari, Brady, Lord, & Tager-Flusberg, 2013).

Despite the large proportion of minimally verbal individuals with ASD, the vast majority of research on cognition and brain function in ASD focuses on high-functioning individuals with age-appropriate or only mildly-impaired language and cognitive abilities. This reflects the practical difficulties of testing these profoundly affected individuals (Tager-Flusberg & Kasari, 2013), as well as concerns that results may be compromised by failure to understand task instructions or comply with task demands. However, it is questionable whether insights gained from studies of linguistically able individuals with ASD may be extrapolated to those who are minimally verbal. As such, the lack of research on minimally verbal individuals with ASD has implications not only for the understanding of this group, but also for the broader understanding of ASD.

To conduct research with minimally verbal children with ASD, it is important to develop valid measures of functioning that do not depend upon the ability to understand task instructions or comply with task demands. In principle, neurophysiological techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) are well suited to this purpose (Tager-Flusberg & Kasari, 2013). Electroencephalography reflects electrical activity from populations of synchronously firing neurons (Luck, 2005), while

MEG measures the corresponding magnetic fields (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993; Hari, Parkkonen, & Nangini, 2010). Both techniques are safe, non-invasive, and silent, and can provide insights into the neural mechanisms underpinning cognitive function. Importantly, EEG and MEG responses can often be recorded passively while the participant is engaged in another activity, thereby avoiding concerns about confounding influences of poor task understanding and poor attention.

MEG and EEG offer complementary strengths. MEG has superior spatial resolution because the brain's magnetic fields are not 'smeared' or distorted by the brain, scalp, and skull, and are less prone to physiological noise (Hari et al., 2010; Hämäläinen et al., 1993). This allows for cleaner extraction of brain responses that are simpler to interpret. MEG also requires minimal set up and there is no physical contact with sensors, making it well tolerated by verbal children with ASD (Brock, 2013; Hari et al., 2010; Roberts et al., 2008). Compared to MEG, EEG is more tolerant of participant movement. It is also much cheaper and more widely available, making it the only realistic tool for large-scale multi-site studies and, ultimately, for clinical applications.

Despite their considerable potential, MEG and EEG studies of profoundly affected individuals with ASD are surprisingly rare. To date, such studies have focused on auditory processing. Using MEG, Tecchio et al. (2003) tested 8- to 32-year-old autistic individuals with "moderately to severely impaired" verbal communication (according to the Childhood Autism Ratings Scale). Relative to typically developing control participants, they showed a normal M100 response to the onset of tones, but a weak or absent mismatch response to rare sounds in the sequence. In contrast, Ferri et al. (2003) found no evidence of group differences in the mismatch response or subsequent P3a response. Participants were described as having "low functioning autism" and "mental retardation", but unfortunately no further details were provided regarding their language proficiency.

The current paper adds to this sparse literature on auditory processing in minimally

verbal individuals with ASD. We present a case report of GM, a minimally verbal girl with ASD and cerebral palsy who, at the time of writing, has never spoken. When GM was 8 years and 10 months old, we had the opportunity to measure her brain responses to vowels sounds and complex tones using MEG. Two years later, we were able to re-test GM, this time using a novel "gaming" EEG headset that has been adapted for research purposes. Together, the two experiments indicate that GM has a highly unusual pattern of brain responses, characterised by atypically strong responses to nonspeech sounds, but weak responses to speech. This preliminary case report demonstrates, we believe, the feasibility and potential of both EEG and MEG for the study of minimally verbal individuals with ASD as well as those with cerebral palsy.

Case description

GM is a young girl with ASD and cerebral palsy. At the time of testing for Experiment 1, she was 8 years and 10 months old. By the time of Experiment 2, she was 10 years and 10 months old. She has never spoken, and currently uses an augmentative and alternative communication system on the iPad. She attends a school for children with special needs. Other than her cerebral palsy, GM has no history of brain injury or epilepsy. She has no history of ear infections, and was not on medications at the time of either testing session. Her family speaks Australian English at home.

GM was diagnosed with cerebral palsy (spastic diplegia) aged 18 months. She has global developmental delay and did not walk until after her third birthday. Her mother reports that, as an infant, she had good eye contact and social communication but lost this at around 18 months. Her diagnosis of DSM-IV Autistic Disorder was conferred by a developmental paediatrician at 46 months. On the 'Lifetime' scale on the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003), she scored 29, well above the threshold of 15 for suspected ASD. Module 1 of the Autism Diagnostic Observation Schedule (ADOS, Module 1; Lord, Rutter, DiLavore, & Risi, 2002) was

administered but discontinued, because she failed to engage in any of the activities and started to show signs of frustration and distress.

Cognitive abilities and adaptive behaviour

Due to GM's severe communication challenges, we also had difficulty administering the standard test battery that is given to other children in our studies (see Participants section of Experiment 1). However, GM's mother was able to provide a report from a Clinical Psychologist and Senior Clinical Neuropsychologist of an assessment conducted at age 8 years and 2 months using modified procedures. Relevant sections from the report are reproduced below, with the caveat, noted by the clinicians, that the results of testing may have under-represented GM's true abilities.

"The administration of assessment protocol was adapted due to the severity of [GM's] attention and expressive language difficulties. Task instructions were often repeated and the examiners pointed to relevant stimuli to help [GM] focus. Tasks were selected that allowed [GM] to point to her answer and tasks that required a single word or two word response, that [GM] could type on a computer or her iPad…

"The nonverbal subtests on the [Wechsler Intelligence Scale for Children] were administered to assess [GM's] level of intellectual functioning… The Block Design subtest could not be administered because of [GM's] motor difficulties... [GM's] visual processing and abstract reasoning ability were found to fall within the 'extremely low' range. The results indicated that [GM's] performance/nonverbal skills were consistent with mild to moderate level of intellectual disability…

"[GM's] understanding of vocabulary was measured with the [Peabody Picture Vocabulary Test - 4th Edition]… On formal testing, her performance was consistent with a 3-4 year age level…

"[GM's mother] completed the [Adaptive Behaviour Assessment System – 2nd Edition] which assesses a child's level of independence in everyday living including the

areas of communication, daily and community living skills, social and leisure, functional pre-academics, and motor skills. [GM's] skills overall were in the significantly delayed or 'extremely low' range. There was no significant variation evident in her overall level of functioning".

Auditory sensory processing

Given the study's focus on auditory processing, GM's mother was asked to complete the Short Sensory Profile (McIntosh, Miller, Shyu, & Dunn, 1999), a parent questionnaire that addresses the sensory processing of the child in everyday situations. GM scored within the typical range for the Tactile, Taste/Smell, Movement and Visual/Auditory Sensitivity items. She scored within the Probable Difference range for the Underresponsive/Seeks Sensation and Auditory Filtering items and within the Definite Difference range in the Low Energy/Weak section, which relates to under-responsiveness to vestibular and proprioceptive sensation (Lane, Dennis, & Geraghty, 2011). Within the auditory items, she was reported to have never responded negatively to unexpected or loud noises, nor to hold hands over ears, or have trouble completing tasks when the radio is on. However, she was reported to be occasionally distracted or have trouble functioning in noisy environments. Further, she was reported to not hear people, not respond to her name being called, and have difficulties with attention.

Experiment 1

In Experiment 1, we used MEG to investigate GM's brain responses to speech and nonspeech sounds. Procedures for this experiment and Experiment 2 were approved by the Macquarie University Human Research Ethics Committee. Written consent was obtained from parents of all participants, who were given a modest amount of money, a small prize, and a certificate for their participation.

Participants

At the time of testing, GM was 8 years and 10 months old. Her brain responses

were compared to those of 18 typically developing (TD) children (15 boys) and 13 verbal children with ASD (11 boys), aged between 6 and 14 years, who were tested as part of a separate study (see Paper 1). All children spoke English as a first language and had normal hearing as determined using an Otovation Amplitude T3 series audiometer.

All children with ASD had reports from psychologists or paediatricians confirming their DSM-IV and/or ICD-10 diagnosis of an ASD. Those who had been diagnosed more than five years ago were administered the ADOS to confirm a current diagnosis of ASD. In addition, they all scored above the Autism cut-off on the SCQ. Language scores on the PPVT, TROG-II, and CELF Sentence Repetition varied widely as shown in Table 1.

Typically developing (TD) children scored below the Autism cut-off on the SCQ, and reported no history of brain injury, ASD, language impairment, or developmental disorders in their family.

Table 1

Standardised Neuropsychological Test Battery Results for Verbal Children with Autism Spectrum Disorders (ASD) Typical Development (TD)

	ASD (*N* = 13)		TD (*N* = 18)	
	M (SD)	*Range*	*M (SD)*	*Range*
Age (years)	10.82 (1.72)	7.75-13.25	10.02 (2.39)	6.67- 14.58
Matrix reasoning (Wechsler, 2003) [a]	8.71 (3.52)	4-14	12.44 (2.28)	9-16
Receptive vocabulary (L. M. Dunn & Dunn, 2007) [b]	98.00 (23.96)	61-160	121.39 (15.45)	92-167
Receptive Grammar (D. V. Bishop, 2003) [b]	85.29 (18.49)	55-111	106.67 (8.94)	85-123
Sentence repetition (Semel, Wiig, & Secord, 1987) [a]	5.71 (3.69)	1-11	10.72 (2.27)	7-15
Social Communication Questionnaire	24.57 (6.43)	17-37	2.33 (1.82)	0-6

Notes: a Scaled scores with population means and standard deviations of 10 and 3; *b.* Standard scores with population means and standard deviations of 100 and 15.

Stimuli

Stimuli were 200-ms long with 5-ms ramps at the start and end to avoid clicks and distortions to the sounds. The speech stimulus was a natural sounding English vowel /a/ (McArthur, Atkinson, & Ellis, 2009). The nonspeech stimulus was created using Adobe Audition to match the first three formants of the speech sound (see Table 2 for stimuli characteristics). The main difference between the two sounds was the presence of a

fundamental frequency (F0) in the speech stimuli, which gave the speech sounds their 'speechiness'.

Table 2

Speech and Nonspeech Stimuli Acoustic Parameters

	Speech			Nonspeech		
Formant	Hertz	Milliseconds	Bandwidth	Hertz	Milliseconds	Bandwidth
F0	106-119	5-20	NA	NA	NA	NA
	120	25-80	NA	NA	NA	NA
	119-179	85-200	NA	NA	NA	NA
F1	700	5-200	70	700	5-200	NA
F2	1560	5-200	130	1560	5-200	NA
F3	2430	5-200	320	2430	5-200	NA

Stimuli were presented binaurally at 75 dB SPL via earphones attached to rubber air tubes (Model ER-30, Etymotic Research Inc., Elk Grove Village, IL). Children were presented with eight blocks of 100 speech stimuli interleaved with eight blocks of 100 nonspeech stimuli. The stimulus onset asynchrony (SOA) was jittered with a uniform distribution between 900 and 1100 ms. The stimuli were presented in an oddball paradigm originally designed to elicit a mismatch field. Each block of 100 sounds included 85 frequently occurring 'standard' sounds and 15 rarely occurring 'deviant' sounds (a 10% increase in the frequency of F1, F2, and F3 relative to the standard sound). However, like other researchers, we found that the mismatch response was not reliably elicited at the individual level (Kurtzberg, Vaughan, Kreuzer, & Fliegler, 1995; Mahajan & McArthur, 2012; McArthur, Bishop, & Proudfoot, 2003; Uwer & von Suchodoletz, 2000). Thus, our analyses focused on the obligatory brain responses to the onset of the standard stimuli.

MEG recording

MEG data were recorded using 160 coaxial first-order gradiometers with a 50 mm baseline (Model PQ1160R-N2, KIT, Kanazawa, Japan; Kado et al., 1999; Uehara et al., 2003). MEG data were acquired with a sampling rate of 1,000 Hz and filter bandpass of 0.03–200 Hz. Prior to MEG recording, each child was fitted with an elasticised cap containing five marker coils. The positions of the coils and the shape of the participant's head were measured with a pen digitiser (Polhemus Fastrack, Colchester, VT). Head position was measured with the marker coils before and after each MEG recording, and children were visually monitored for head movements. Children who exceeded head-movement of 5 mm were excluded from further analyses. During the recording, participants watched a silent subtitled DVD of their choice projected on a screen on the ceiling of the MEG room while lying on a comfortable bed inside the magnetically shielded room.

MEG data processing

Using BESA 6.0 (MEGIS Software GmbH, Grafelfing, Germany), the MEG data were filtered between 0.1 and 30 Hz, epoched from -100 ms pre-stimulus onset to 500 ms post-stimulus onset, and baseline corrected from -100 to 0 ms. Epochs with gradient artefacts greater than 5336 fT/cm were excluded from further analysis. All participants had at least 75% artefact-free epochs for each condition. On average, there were 542 accepted epochs for speech sounds and 538 for nonspeech sounds in the control group. For GM, there were 448 accepted epochs for speech sounds and 494 for nonspeech sounds.

Data were first analysed at the sensor level by computing the Global Field Power (GFP, Lehmann & Skrandies, 1980). This involved transforming the speech and nonspeech waveforms for each of the 160 sensors to absolute values and then averaging across the 160 channels (cf. Kasai et al., 2005). This procedure avoids bias that may arise from picking a group of channels and complements analyses conducted in source space.

Magnetic GFP also strongly corresponds with fitted dipoles in terms of strength and latency, and is considered a good representation of underlying brain activity from the sources (Kasai et al., 2002, 2003).

Data were also analysed in source space using BESA 6.0. For each participant, we first averaged the sensor data across the speech and nonspeech conditions. Two dipoles were initially placed in bilateral Heschl's gyrus (according to the template brain) and then fitted freely (location and orientation) subject to the constraint that their locations remained symmetrical. For most participants, the 80-110ms window, corresponding to the M100 response was used for dipole fitting. However, in some cases, it was necessary to extend the time window down to 70 ms or up to 160ms. Separate speech and nonspeech source waveforms were then extracted from the left and right hemisphere dipoles.

Results and Discussion

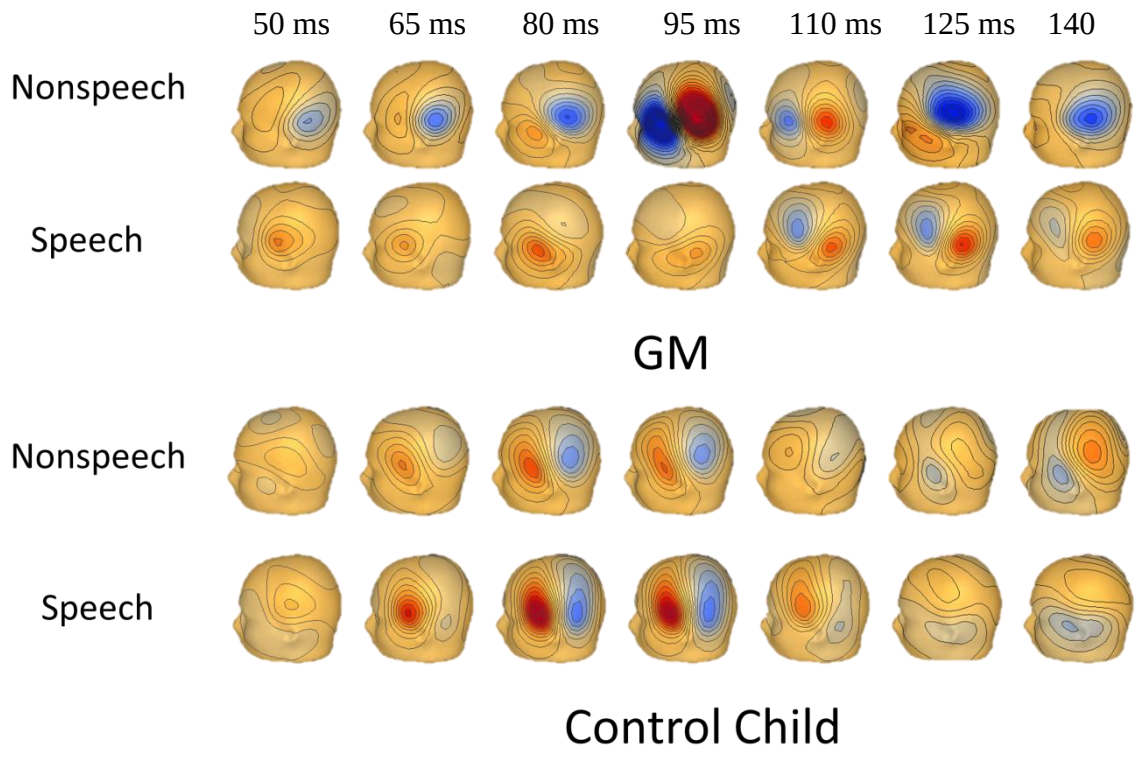

Figure 1. Timeline of M50/M100 magnetic flux activity showing brain activity from left hemisphere sensors to speech and nonspeech stimuli. The top two rows are GM and the bottom two rows are of an age-matched typically-developing child.

Figure 1 shows a timeline of GM's magnetic flux map for speech and nonspeech responses. Note that compared to the age-matched typically developing child in Figure 1, her response to nonspeech was much earlier and larger than her response to speech.

Figures 2 and 3 show each participant's sensor waveforms to speech and nonspeech sounds. Again, there was a discrepancy between GM's double-peaked response to nonspeech stimuli and her virtually flat response to speech. In contrast, the other participants showed similar responses to speech and nonspeech stimuli. Note, however, that the participants differed widely in both the morphology of the waveforms and their overall magnitude. While this may partly reflect differences in brain activity, it may also depend on the child's position in the MEG helmet and the size of their heads. We therefore used intra-class correlations (ICCs; cf. Bishop & McArthur, 2004, 2005) to quantify the similarity between each participant's speech response and their own nonspeech responses. Initially, we included the whole epoch (0 – 500 ms) in the ICC calculations. However, we also considered a narrower 65 - 165 ms window, which incorporated the obligatory M50 and M100 responses (see Paper 1). ICC scores were Fisher-z transformed to improve linearity for parametric statistics.

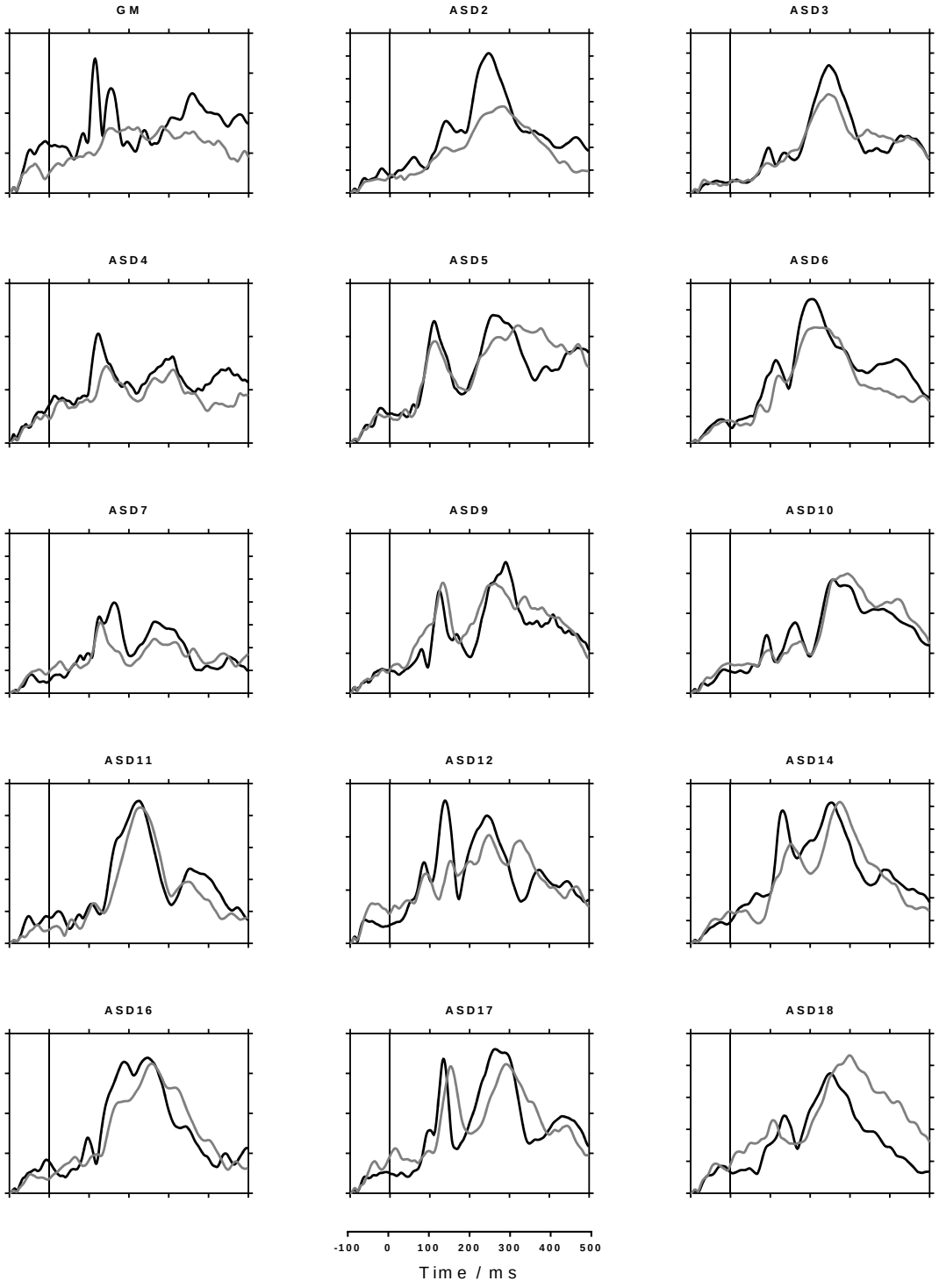

Figure 2. Sensor waveforms for GM and all verbal children with autism spectrum disorders (ASD). Grey lines indicate response to speech and black lines indicate nonspeech response. Each tick on the vertical axis represents 10 femtoTesla.

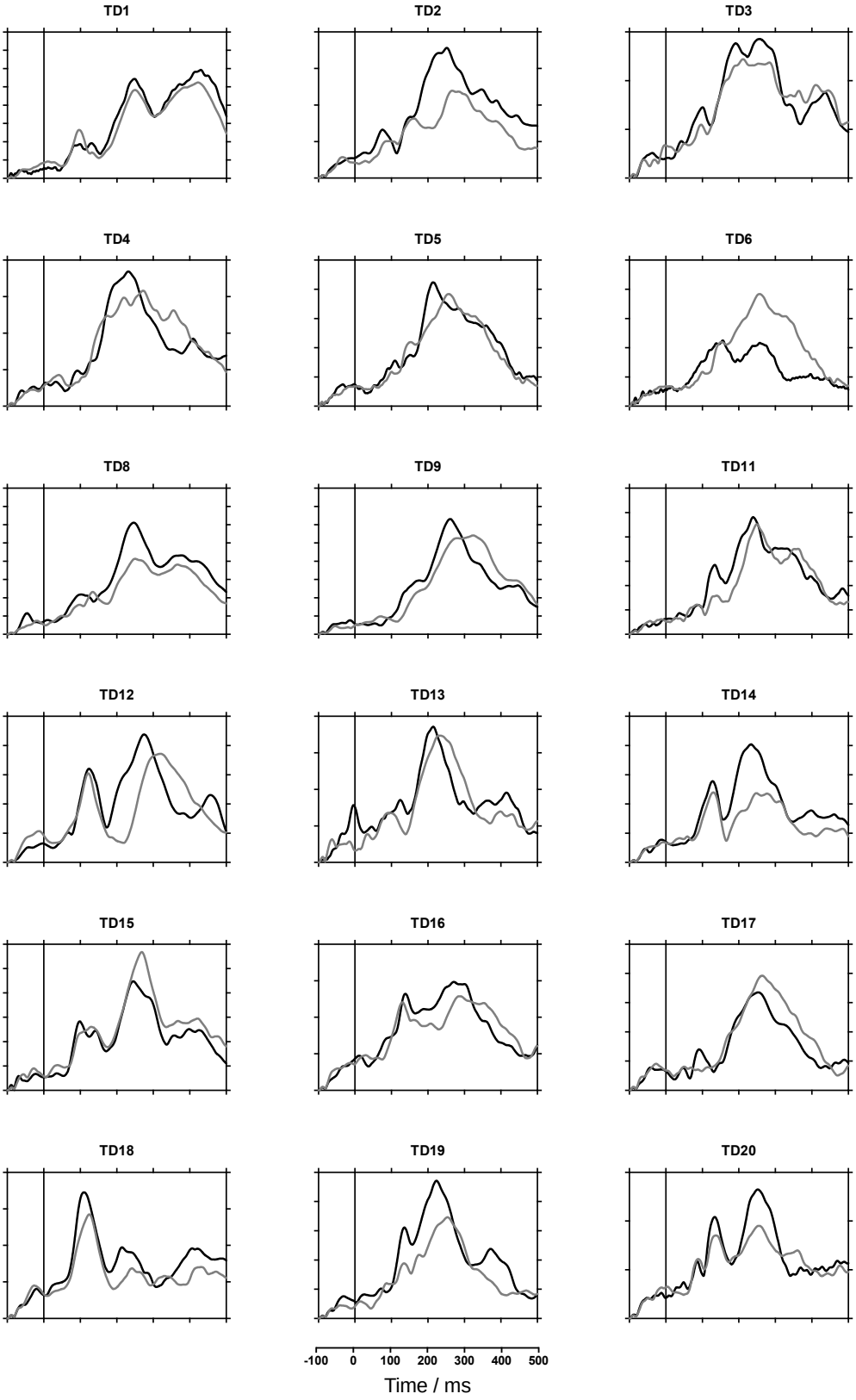

Figure 3. Sensor waveforms for GM and children with typical development (TD). Grey lines indicate response to speech and black lines indicate nonspeech response. Each tick on the vertical axis represents 10 femtoTesla.

We compared GM's ICCs to those of children in the TD and ASD comparison groups using SingLims (Crawford, Garthwaite, & Porter, 2010). SingLims assumes the comparison participants to be a representative sample of the population, and uses modified t-tests to estimate the "abnormality" of a case's scores and the percentile ranking of the case (i.e., the percentage of the control population exhibiting a lower score than the case). Tables 3 and 4 show the SingLims test results, and point and interval estimates of effect size and abnormality for GM's scores, compared to the TD and ASD comparison groups respectively. GM's ICCs were significantly lower than both control groups for both the 65 – 165 ms and 0 – 500 ms time periods, in each case placing her in the bottom 5% of the population.

Table 3

Table of Results Comparing GM to the Typically Developing (TD) Control Group

	TD group			GM	GM vs TD		Percentile		Effect size	
	N	*Mean*	*SD*		*t*	*p*	Point	95% CI	Point	95%CI
Sensor waveforms										
0–500 ms	18	1.11	0.39	-0.11	-3.04	0.00	0.37	0.00 to 2.38	-3.13	-4.26 to -1.98
65–165 ms	18	0.73	0.48	-0.16	-1.81	0.04	4.44	0.45 to 14.17	-1.85	-2.62 to -1.07
Source waveforms										
LH 65–165 ms	18	0.45	0.52	-0.66	-2.08	0.03	2.66	0.15 to 10.08	-2.13	-2.97 to -1.28
RH 65–165 ms	18	0.54	0.63	0.13	-0.63	0.27	26.74	12.44 to 44.73	-0.65	-1.15 to -0.13

Notes: Percentile point shows percentage of the control population exhibiting a lower score than GM. The 95% confidence interval (95% CI) denotes the certainty of the point percentile (Crawford et al., 2010), or the certainty of the rarity of GM's scores. The 95% CI in effect size denotes the certainty or credibility of the effect size of the differences between GM and controls.

Table 4

Table of Results Comparing GM to the Autism Spectrum Disorders (ASD) Control Group

	ASD group			GM	GM vs ASD		Percentile		Effect size	
Measure	*N*	*Mean*	*SD*		*t*	*p*	Point	95% CI	Point	95%CI
Sensor waveforms										
0 – 500 ms	14	0.98	0.54	-0.11	-1.95	0.03	3.65	0.16 to 14.06	-2.02	-2.94 to -1.08
65 – 165 ms	14	0.58	0.35	-0.16	-2.04	0.03	3.09	0.11 to 12.65	-2.11	-3.06 to -1.14
Source waveforms										
LH 65 – 165 ms	14	0.70	0.50	-0.66	-2.63	0.01	1.04	0.00 to 6.04	-2.72	-3.87 to -1.55
RH 65 – 165 ms	14	0.55	0.5	0.13	-0.81	0.22	21.58	7.47 to 41.49	-0.84	-1.44 to -0.21

Notes: Percentile point shows percentage of the control population exhibiting a lower score than GM. The 95% confidence interval (95% CI) denotes the certainty of this point percentile (Crawford et al., 2010), or the certainty of the rarity of GM's scores. The 95% CI in effect size denotes the certainty or credibility of the effect size of the differences between GM and controls.

Figure 4 shows the results of the source analysis for GM. It suggests that the striking differences between GM's speech and nonspeech sensor waveforms originate from the left hemisphere. As for the sensor analysis, we calculated Fisher z-transformed ICCs to

index the similarity of each child's nonspeech and speech dipole waveforms, for left and right hemisphere sources. As the dipoles used for source extraction were oriented to the M50/M100 response, we only report ICCs for the corresponding 65-165 ms window. SingLims analyses (Tables 3 and 4) showed that GM had significantly reduced ICCs for the left hemisphere, again placing her in the bottom 5% of the population. Her right hemisphere responses were within the normal range.

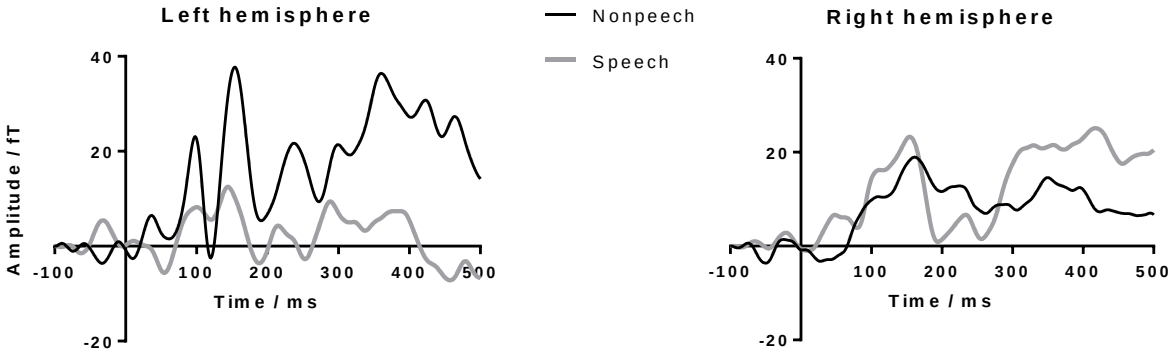

Figure 4. GM's source waveforms for speech and nonspeech stimuli measured from left and right hemisphere sources approximating auditory cortex. Grey lines indicate response to speech and black lines indicate nonspeech response. Vertical axis represents amplitude in femtoTesla.

To summarise, GM showed a striking dissociation between her M50/M100 responses to speech and nonspeech sounds, which was not shown by either TD children or other verbal children with ASD. This appeared to originate in her left auditory cortex. However, a potential concern was that GM's atypical brain responses might arise simply from methodological artefacts. Thus, in a follow-up experiment conducted two years after Experiment 1, we took the opportunity to re-test GM, this time using a "gaming" EEG system that produces comparable data to conventional research EEG systems.

Experiment 2

Participants

At the time of testing for Experiment 2, GM was 10 years and 10 months old. Her auditory brain responses to nonspeech sounds were compared to those of 21 TD children (11 females, 10 males) aged between 6 and 12 years, tested using the same procedures as part of a validation study for the EEG system. The mean age of TD participants was 9.23 years (SD = 1.78). Participants had normal hearing and vision, and no history of developmental disorders or epilepsy.

Stimuli

Participants were presented 566 standard tones (175-ms 1000-Hz pure tones with a 10-ms rise and fall time; 85% of trials) and 100 deviant tones (175-ms 1200-Hz pure tones with a 10-ms rise and fall time; 15% of trials). Deviant tones were included to calculate the mismatch response. However, in line with Experiment 1, analyses focused on the obligatory auditory brain responses to standard sounds. Stimuli, separated by a jittered SOA of 900 to 1100 ms, were presented binaurally at a comfortable listening volume through speakers.

EEG recording and analysis

Participants were seated in a comfortable chair and watched a silent video whilst ignoring the tones. Auditory brain responses were measured using an Emotiv EPOC gaming EEG system that has previously been validated against a research-grade Neuroscan EEG system (Badcock et al., 2013). The sensors in the headset were adjusted on the head until suitable connectivity was achieved as indicated by the TestBench software, which adds a small modulation to the feed-forward signal, and measures the size of the signal back from each channel. The experiment took 10–15 minutes.

The Emotiv EEG system uses gold-plated contact-sensors fixed to flexible plastic arms of a wireless headset. The headset included 17 sites, aligned with the 10–20 system:

AF3, AF4, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, FC4, M1, and M2. One mastoid (M1) sensor acted as a ground reference point to which the voltage of all other sensors were compared. The other mastoid (M2) was a feed-forward reference that reduced external electrical interference. The signals from the other 14 scalp sites (channels) were high-pass filtered with a 0.16 Hz cut-off, pre-amplified and low-pass filtered at an 83 Hz cut-off. The analogue signals were then digitised at 2048 Hz. The digitised signal was filtered using a 5th-order sine notch filter (50–60 Hz) and low-pass filtered and down-sampled to 128 Hz. The effective bandwidth was 0.16–43 Hz.

The Emotiv EEG system was modified to send markers to the EEG to indicate the onset of each stimulus (Thie, Klistorner, & Graham, 2012). This was achieved using a custom-made transmitter that converted the onset and offset of each tone into a positive and negative electrical signal. These signals were injected into the O1 and O2 channels using an infrared triggering system. The positive and negative spikes in the O1 and O2 EEGs were processed offline in Matlab. A between-channels difference greater than 50 mV was coded as a stimulus onset or offset. The event marker had at a constant time interval (20 ms delay of the transmitter module) prior to the point of positive and negative signal cross-over. Stimulus markers were recombined with the EEG data.

The resultant EEG was processed offline using EEGLAB version 11.0.4.3b (Delorme & Makeig, 2004). The EEG in each channel was bandpass filtered from 0.1 to 30 Hz, and then divided into epochs that started 102 ms before the onset of each stimulus and ended 500 ms after the onset of the same stimulus. Each epoch was baseline corrected from 102 to 0 ms. Artefacts were rejected using EEGLAB's automatic rejection ('pop_autorej') function, with a 150 mV threshold for extreme values and the default settings. For the standard tone, this left us with a mean of 525 (SD = 36, min = 395, max = 565) epochs for the control group, and 428 epochs for GM. Accepted epochs to the standard tone were averaged together to create a standard auditory ERP waveform for GM

and each control.

Results and Discussion

Figure 5 shows GM's responses to the standard tones recorded from two electrodes, AF3 (left frontal) and AF4 (right frontal) that produced the clearest response in the TD control participants. Consistent with her atypically large MEG response to nonspeech stimuli in Experiment 1, GM showed a strikingly strong and early response to the tone stimuli, particularly for the left frontal electrode. This was clearly outside the range of any of the TD control participants. Thus, GM's unusually large brain response to nonspeech stimuli appears to be a stable and replicable characteristic of her cortical response to a range of nonspeech stimuli.

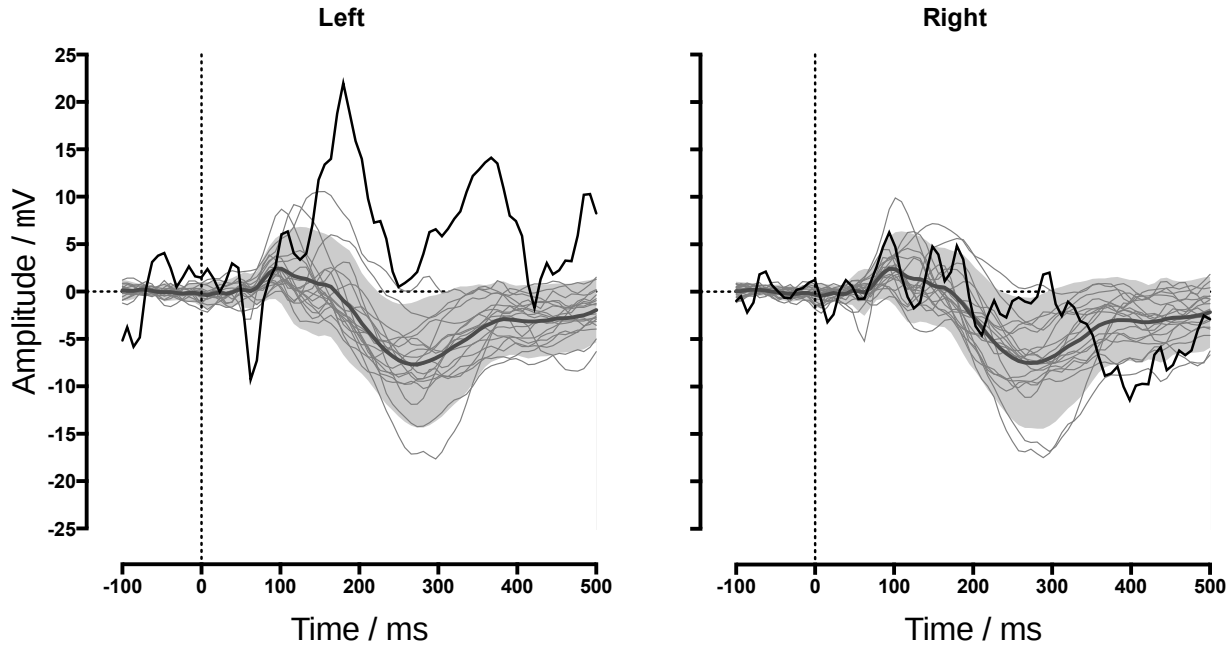

Figure 5. Event-related potentials (ERPs) to nonspeech sounds measured from frontal electrodes AF3 (left) and AF4 (right). Black line shows GM's response. Grey region indicates the average response of children with typical development (TD) for +/- 1.64 SD (considered the "normal" range). Light grey lines show responses of individual TD children.

General Discussion

Minimally verbal individuals represent a significant proportion of the autistic population and yet are typically excluded from research on cognition and brain function. In the current study, we used MEG and EEG to measure the brain responses to auditory stimuli of a minimally verbal child with ASD. The initial MEG study in Experiment 1 revealed a striking dissociation between her auditory sensory encoding of speech and nonspeech sounds. Specifically, GM had relatively strong and early responses to nonspeech, but unusually weak responses to speech sounds. MEG source analysis indicated that these differences arose in her left hemisphere. We were able to demonstrate statistically that this discrepancy between speech and nonspeech stimuli was highly unusual. Whether compared to typically developing children or other verbal children with ASD, GM's response similarity for speech and nonspeech fell into the bottom 5% of the population.

In Experiment 2, we replicated the finding that GM shows unusually strong response to nonspeech stimuli. This was observed despite the fact she was tested two years after Experiment 1 using a different neurophysiological technique (EEG rather than MEG), using different stimuli (pure tones rather than complex tones), as well as a different control sample. This successful replication indicates that GM's atypical responses to nonspeech sounds are genuine and not merely a statistical fluke or consequence of methodological artefact.

GM's atypical responses to nonspeech sounds in both experiments might be considered a neural correlate of atypical auditory processing that is widely reported amongst individuals with ASD (Boddaert et al., 2004; Gervais et al., 2004). Autobiographical accounts of individuals with ASD often include descriptions of atypical sensory experiences, particularly in relation to sounds (Ben-Sasson et al., 2009; Bettison, 1996; Grandin & Scariano, 1986; Reynolds & Lane, 2008). These accounts are supported

by parental reports, clinical observations, and by enhanced performance on certain psychoacoustic tests (Bonnel et al., 2003; Bonnel et al., 2010; Heaton, Hudry, Ludlow, & Hill, 2008; Jones et al., 2009; Tomchek & Dunn, 2007). Surprisingly, then, GM appears to show little evidence of hyper-responsiveness to auditory stimuli in everyday life, as documented by her mother's responses on the Short Sensory Profile. Given GM's communication challenges, we were unable to obtain a self-report of her sensory experiences. Thus it remains an open question what the subjective experience of her atypical cortical responses might be.

Clearly, the other intriguing aspect of GM's data is her attenuated response to speech stimuli in the MEG experiment. Again, there are obvious concerns about potential artefacts or excessive noise in GM's response. However, given that speech and nonspeech stimuli alternated in short blocks, it is difficult to think of any artefact that would lead to noisier data in one condition but such clean and strong responses in another. Nor is it clear how such an artefact would result in a dissociation between speech and nonspeech in the left hemisphere but not in the right.

One interpretation is that GM's brain "switches off" to speech stimuli. This would be consistent with the theories of social deficit or an impairment in social motivation and cognition in ASD (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Dawson et al., 2004; Klin, 2003) and with previous ERP studies suggesting that children with ASD show a difference in the attentional orienting to speech and nonspeech sounds, particularly when they are not explicitly required to attend to the sounds (Čeponienė et al., 2003; Lepistö et al., 2005; Lepistö et al., 2006; Whitehouse & Bishop, 2008). However, these previous studies have focused on the later mismatch negativity and P3 components of the auditory ERP, whereas the striking differences between speech and nonspeech in GM's brain responses were apparent much earlier in the waveform, during the 'obligatory' M50/M100 components.

This in turn suggests that GM's differential response to speech and nonspeech sounds reflects her brain's sensitivity to the acoustic differences between the two stimuli.

The major difference between the speech and nonspeech stimuli is the presence of the fundamental frequency (F0) in the speech stimuli. This serves to give a sound its 'speechness' and provides pitch cues for conveying linguistic and emotional prosody as well as information about speaker identity (see McCann & Peppé, 2003; Peppé, McCann, Gibbon, O'Hare, & Rutherford, 2007 for review). Perhaps most importantly, the fundamental frequency also provides a vital cue for segregating speech from background noise in natural listening environments (e.g., Bronckhorst, 2000). Thus, a neural impairment affecting the processing of the fundamental frequency might be expected to have profound implications for the development of speech perception.

It is important to note that GM also has a diagnosis of cerebral palsy, which clearly sets her apart from other minimally-verbal autistic children. The nature of the relationship between ASD and cerebral palsy is unclear and difficult to tease apart (Zwaigenbaum, 2014). Although the incidence of ASD is considerably higher amongst individuals with cerebral palsy (approximately 6%; Christensen et al., 2014) than it is in the general population, the majority of individuals with cerebral palsy do not meet ASD criteria. Likewise, speech and language abilities are affected in the majority of individuals with cerebral palsy, but the complete absence of speech is relatively rare (Odding, Roebroeck, & Stam, 2006). Nevertheless, future studies could consider including a comparison group of children with cerebral palsy, but without Autism, to further understand if this link between language and speech processing is specific to those with Autism.

Clearly, GM represents an unusual case and it is unclear the extent to which her atypical brain responses might generalise either to other minimally verbal children with ASD or to others with cerebral palsy. Nonetheless, the current study represents an important proof of concept, demonstrating that it is possible in practice to elicit brain

responses, using both MEG and EEG, from minimally verbal children with ASD. Future studies can take advantage of the complementary strengths of these two techniques and begin to answer vital questions pertaining to cognition and brain function within this much-neglected subgroup of the ASD population.

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Chapter 4

The magnetic acoustic change complex: A robust and efficient neural measure of auditory discrimination

This chapter has been submitted for publication as:

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Abstract

Objective: Electrophysiological studies of auditory processing disturbances in a range of clinical conditions have typically employed the mismatch negativity (MMN) as an objective test of auditory discrimination. However, interpretation of the MMN is complex and the response has been found to have questionable reliability. The Acoustic Change Complex (ACC), a P1-N2-like response to changes in a continuous sound, has been suggested as a purer and more efficient test of auditory discrimination. The aim of this study was to extend the ACC paradigm to magnetoencephalography (MEG) and compare the signal-to-noise ratio (SNR) and time-efficiency of the magnetic ACC (mACC) to the mismatch field (MMF).

Methods: Brain responses of 17 normal hearing adults were recorded using MEG during a mACC paradigm and an optimal MMF paradigm. Both paradigms involved the same linguistically relevant pitch and vowel changes.

Results: Signal-to-noise ratio for the mACC was overall better than for the MMF. While the SNR for MMF was significantly higher to vowel than pitch change, the mACC demonstrated similar SNRs for both pitch and vowel change.

Conclusions: The mACC paradigm consistently elicited auditory discrimination responses of high SNR and is a promising alternative to the MMF in the study of auditory discrimination. While we used an optimal MMF design, the mACC paradigm can be improved to further increase its efficiency.

Significance: The mACC has a clear advantage over the MMF as pure test of auditory discrimination. This is particularly true in studies of child and clinical populations due to its high SNR and corresponding high efficiency. However, studies using both the MMF and mACC paradigms may be well placed to distinguish between impairments occurring at different stages of auditory processing.

The Magnetic Acoustic Change Complex: A Robust and Efficient Neural Measure of Auditory Discrimination

Introduction

Our ability to discriminate sounds is a prerequisite for developing spoken language (Ponton, Eggermont, Kwong, & Don, 2000). It differs from mere detection of a sound in that it enables different meanings to be attributed to different stimuli (Picton & Taylor, 2007). While late cortical auditory evoked potentials such as the obligatory P1-N1-P2 responses are taken to show that the brain has detected a sound, auditory discrimination is typically indexed via the Mismatch Negativity (MMN) or its magnetic counterpart, the mismatch field (MMF), sometimes referred to as the MMNm (Alho, 1995; Hari et al., 1984). The MMN/MMF is regarded as the auditory discrimination paradigm of choice in clinical research, having been used in studies of people with autism, attention deficit hyperactivity disorder, schizophrenia, dyslexia, auditory processing disorder, Parkinson's disease, Alzheimer's disease, Tourette's syndrome and childhood cancer, as well as comatose patients and cochlear implants users (see Näätänen, 2003, and Näätänen & Escera, 2000, for reviews). It has played an especially important role in the field of language and literacy disorders, where a weak or absent MMN is assumed to reflect poor sound discrimination, with cascading effects on speech perception and language development (Kujala, Tervaniemi, & Schroger, 2007). However, despite its popularity, the MMN/MMF paradigm suffers a number of criticisms, including unclear interpretation and questionable reliability (May & Tiitinen, 2010), particularly in clinical and child populations (Bishop, 2007). Thus, in the current study, we compared the MMF with an alternative measure of auditory discrimination at the cortical level - the magnetic acoustic change complex (mACC).

The MMN is elicited in a classic oddball paradigm as a negative-deflecting potential, in response to a different or novel sound (a deviant) occurring within a string of

repetitive sounds (standards; Näätänen & Picton, 1987). It is essentially a difference waveform that can be derived by subtracting the brain responses of the standard from the deviant sounds during the N2 and N2-P3 wave complexes. A major advantage of the MMN auditory discrimination paradigm is that the response can be elicited passively (see Escera, Alho, Schröger, & Winkler, 2000 for review), therefore removing the confounds of attention and participation difficulties that may be present in behavioural testing of infants, young child and special populations.

The validity of the MMN as a measure of discrimination is demonstrated by studies showing that the size of the MMN is related to performance on behavioural discrimination tasks (Amenedo & Escera, 2000; Baldeweg, Richardson, Watkins, Foale, & Gruzelier, 1999; Kujala, 2001; Lang et al., 1995; Winkler, 1999). However, Bishop (2007) noted that, in populations with language and literacy impairments, the MMN and behavioural findings were not always consistent. For example, Shafer, Morr, Datta, Kurtzberg, and Schwartz (2005) found that most children with specific language impairment (SLI) did not show MMNs despite being able to behaviourally discriminate sounds. Similar concerns are also apparent at the group level, with several studies reporting that particular participant groups evidence normal or good behavioural discrimination, despite having absent or poor MMNs (Dalebout & Fox, 2000, 2001; Kurtzberg, Vaughan Jr, Kreuzer, & Fliegler, 1995; Shafer et al., 2005; Sharma et al., 2006; Tervaniemi, Just, Koelsch, Widmann, & Schröger, 2005; Umbricht et al., 2003; Uwer & von Suchodoletz, 2000). Other studies show group differences in the MMN, despite no group differences in the corresponding behavioural tasks (Bradlow et al., 1999; Gaeta, Friedman, Ritter, & Cheng, 2001; Jaramillo et al., 2001; Kozou et al., 2005). Researchers have also reported cases where the MMN could not be identified in adults (Dalebout & Fox, 2001; Lang et al., 1995; Wunderlich & Cone-Wesson, 2001), children (Kurtzberg et al., 1995; Uwer & von Suchodoletz, 2000), pre-schoolers, or infants (Morr, 2002), even for easily discriminable stimuli.

These difficulties are also apparent in the conflicting and contradictory conclusions reached from studies of the same clinical population. For example, in studies of autism, the MMN/MMF has been found to be faster and/or stronger (Ferri et al., 2003; Gomot, 2002; Korpilahti et al., 2007; Lepistö et al., 2005; Lepistö et al., 2006), slower and/or weaker (Jansson-Verkasalo et al., 2003; Kuhl, Coffey-Corina, Padden, & Dawson, 2005; Oram Cardy, Flagg, Roberts, & Roberts, 2005; Seri, Cerquiglini, Pisani, & Curatolo, 1999; Tecchio, 2003) as well as normal (Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1995). Although some of this inconsistency is accounted for by the heterogeneity within autism, such mixed findings could be attributed to the MMN signal itself.

One limitation of the MMN is its low signal-to-noise (SNR) ratio. The MMN amplitude is low compared to background EEG activity (Picton, 1995), particularly in young children and clinical participants (Luck, 2005a) and the subtraction procedure for deriving the MMN means that the residual noise from the standard combines with residual noise from the deviant (Picton et al., 2000; Picton & Taylor, 2007). Because the MMN is based on a memory trace formation, and the deviant can only remain novel if it represents a small proportion of the experiment, a very large number of trials are needed in order to obtain a reliable response to the deviant. Thus, the SNR is highly dependent on the amount of time a participant can remain still and cooperative.

Interpreting the MMN is also difficult because of the complexities of processes underlying its generation. One proposal is that the MMN results from neuronal adaptation and lateral inhibition in the auditory cortex (Jääskeläinen et al., 2004; May et al., 1999; Scherg, Vajsar, & Picton, 1989). In addition to multiple generators in the auditory cortex (Jääskeläinen et al., 2004), there are also sources in prefrontal areas (Alain, Woods, & Knight, 1998; Alho, 1995; Giard, Perrin, Pernier, & Bouchet, 1990; Jemel, Achenbach, Müller, Röpcke, & Oades, 2002) which could functionally contribute to the MMN's higher

order perceptual processes over and beyond simple discrimination of the physical differences between two sounds (Pulvermüller & Shtyrov, 2006). These higher order functions include an implicit capacity to store, compare, discriminate, and make predictions and adjustments to understand the auditory environment, and initiate attention switching to different objects in the auditory environment (Bendixen, Schröger, & Winkler, 2009; Escera et al., 2000; Garrido, Kilner, Stephan, & Friston, 2009; Näätänen, 2011; Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000; Todd, Myers, Pirillo, & Drysdale, 2010). In fact, Sussman (2007) stated that the MMN has functions akin to auditory scene analysis and is far more complex than simple sensory discrimination.

In summary, the MMN paradigm has a number of limitations as a test of simple auditory discrimination. However, a promising alternative exists. In 1999, Martin and Boothroyd reported that the obligatory N1-P2 response to the onset of a sound could also be elicited by a change within an ongoing sound. This response, which they termed the Acoustic Change Complex (ACC), was 2.5 times larger than the MMN elicited using the same stimuli. Moreover, every participant produced an ACC response that was clearly visible and identifiable. While the MMN has multiple interpretations, the ACC response is simply interpreted as a change detection response (P1-N1-P2) arising from a change in the activation and deactivation of neural populations within the auditory cortex (Martin, 2010; Martin & Boothroyd, 1999, 2000; Tremblay, Friesen, Martin, & Wright, 2003). Thus, the ACC from a change within a sound would arise from the same mechanisms as the onset response elicited from the start of a sound (Martin, 2010; Nishihara, 2011).

Studies have shown that the ACC is sensitive to a wide range of stimulus changes, including changes in frequency, intensity in sustained tones, as well as speech and speech-like stimuli (Dimitrijevic, Michalewski, Zeng, Pratt, & Starr, 2008; Hari et al., 1984; Kaukoranta, Hari, & Lounasmaa, 1987; Martin, 2010; Martin & Boothroyd, 1999;

Näätänen & Picton, 1987; Nishihara, 2011; Ostroff, Martin, & Boothroyd, 1998; Tremblay et al, 2003; Yamashiro, Inui, Otsuru, & Kakigi, 2011). The ACC has also been found to directly correspond with behavioural measures of intensity and frequency change (He, Grose, & Buchman, 2012; Martin, 2007; Martin & Boothroyd, 2000). For example, He et al. (2012) found that ACC responses to intensity and frequency were comparable, with participants who showed poorer behavioural auditory discrimination also showing higher ACC thresholds. In contrast to the MMN, it also has excellent test-retest reliability (He et al., 2012), even for speech sounds (Tremblay et al., 2003). Moreover, because each trial of the ACC contributes to a response without a prior need for a large number of standards to form a memory trace, testing time can be minimised. Thus, in clinical studies, if the question is whether auditory discrimination per se is impaired, then the ACC holds promise as a quicker and more reliable measure than the MMN.

The current study extended the ACC paradigm to magnetoencephalography (MEG). Magnetoencephalography is a practical tool in research with child and clinical populations because it has a quick and mess-free set-up, and does not involve physical contact with the sensors (i.e., unlike EEG; Hari, Parkkonen, & Nangini, 2010; Roberts et al., 2008). Although EEG and MEG signals both derive from the post-synaptic potentials, there are important differences in their relative sensitivities. Compared to EEG, which picks up both tangential and radial activity, MEG signals are insensitive to radial and deep sources, and thus should be less prone to high noise levels (Hari et al., 2010; Luck, 2005b; Ahlfors, Han, Belliveau, & Hämäläinen, 2010; Ahlfors et al., 2010). Out of the six components that make up the obligatory N1/M100, the three ‘true’ components are triggered by physical aspects of the stimulus, while the other three depend more on the context in which the stimulus occurs (Näätänen & Picton, 1987). Moreover, because the N1 response has been found to have at least six sources, two of which are tangentially oriented (Roberts, Ferrari, Stufflebeam, & Poeppel, 2000), using MEG to elicit a magnetic

ACC constrains the 'true' ACC response to encoding physical changes, and only activity from tangential sources. Together, this should result in a simpler interpretation of the ACC P1-N1-P2 complex. Finally, unlike EEG signals, which take the path of least electrical resistance to the scalp, MEG signals travel in a straight line and are not smeared or distorted by the skull, allowing for more accurate source reconstruction and, of particular relevance to language-related studies, clearer resolution of hemispheric differences (Johnson et al., 2013; Luck, 2005b).

In light of the problems raised in relation to the MMN/MMF, our objective was to compare the MMF with the magnetic ACC (mACC). Specifically, participants were tested in two 15-minute sessions, once with an "optimal" MMF paradigm (Näätänen, 2004) using pitch- and vowel-changes in semi-synthesized speech, and once using a mACC paradigm with the same stimulus changes. By comparing the SNR of the MMF and mACC, we tested if the ACC advantage identified by Martin and Boothroyd (1999) extended to MEG and to linguistically-relevant acoustic changes.

Methods

Subjects

Seventeen adults were initially recruited for the study. One was excluded due to high noise levels (metallic dental work) and another was excluded due to the MEG head-position cap slipping out of position in between blocks (due to the large volume of the subject's hair). Hence, data analyses were based on 15 participants, aged 19 – 40 years (mean = 28.44, SD = 8.24). Fourteen of the 15 participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Participants had a mean score of 11.4 on the Matrices subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1955) – a measure of nonverbal IQ (population mean = 10, SD = 3). None of the participants reported any history of neurological abnormalities and all had normal hearing. Written consent was obtained from all participants and procedures were approved by the

Macquarie University Human Research Ethics Committee. Participants received monetary compensation for taking part in the study.

Auditory Stimuli

Three semi-synthesized speech vowels were generated in Praat (Boersma & Weenink, 2006). The standard sound (e_{low}) was a semi-synthesized /e/ vowel sound. The pitch deviant (e_{high}) differed from the standard in its fundamental frequency, whereas the vowel deviant (u_{low}) had the same fundamental frequency as e_{low}, but differed in the second and third formats, making an /u/ sound. Table 1 shows the formant frequencies of the three sounds.

Table 1

Formant Frequencies in (Hertz) for the Three stimuli. Changes from the Standard (e_{low}) are italicised

	e_{high}	e_{low}	u_{low}
F0	*138*	125	125
F1	280	280	280
F2	2620	2620	*920*
F3	3380	3380	*2200*

The MMF paradigm was modelled on the 'optimal' MMN paradigm using multiple deviants (Kujala, Lovio, Lepistö, Laasonen, & Näätänen, 2006; Näätänen, 2004). Hence, the stimuli were each 75 ms in duration (including 10 ms ramps on and off). Each sequence contained 86% standards (e_{low}), 7% pitch deviants (e_{high}) and 7% vowel deviants (u_{low}) in a pseudo-random order. Within each sequence, at least the first ten sounds were standard sounds in order to create a memory trace and at least two standard sounds were presented between deviants. Stimulus onset asynchrony (SOA) was jittered uniformly

between 450-550 ms. Stimuli were presented in three blocks, each lasting five minutes, resulting in 1600 trials and 15 minutes of testing time.

For the mACC paradigm, a single sound sequence was created, consisting of five units of sound, each of 1500 ms. Each sound sequence (7500 ms) was separated by a 1500 ms silence. Thus throughout the sequence, inter-stimulus intervals (ISIs) were constant at 1500 ms. The order of the sounds in each sequence was: e_{low}, e_{high}, e_{low}, u_{low}, e_{low}. (see Figure 1b). This resulted in an "onset" response (at the start of each sequence), a "pitch up" (from e_{low} to e_{high}), "pitch down" (from e_{high} to e_{low}), "vowel up" (from e_{low} to u_{low}), "vowel down" (from u_{low} to e_{low}) and an "offset" (at the end of each sequence) response respectively. A total of 96 sequences were presented across three blocks, resulting in a total of 480 sounds and 15 minutes of testing time. Figure 1 compares the two paradigms schematically. Order of presentation of the mACC and MMF paradigms was counterbalanced across the participants.

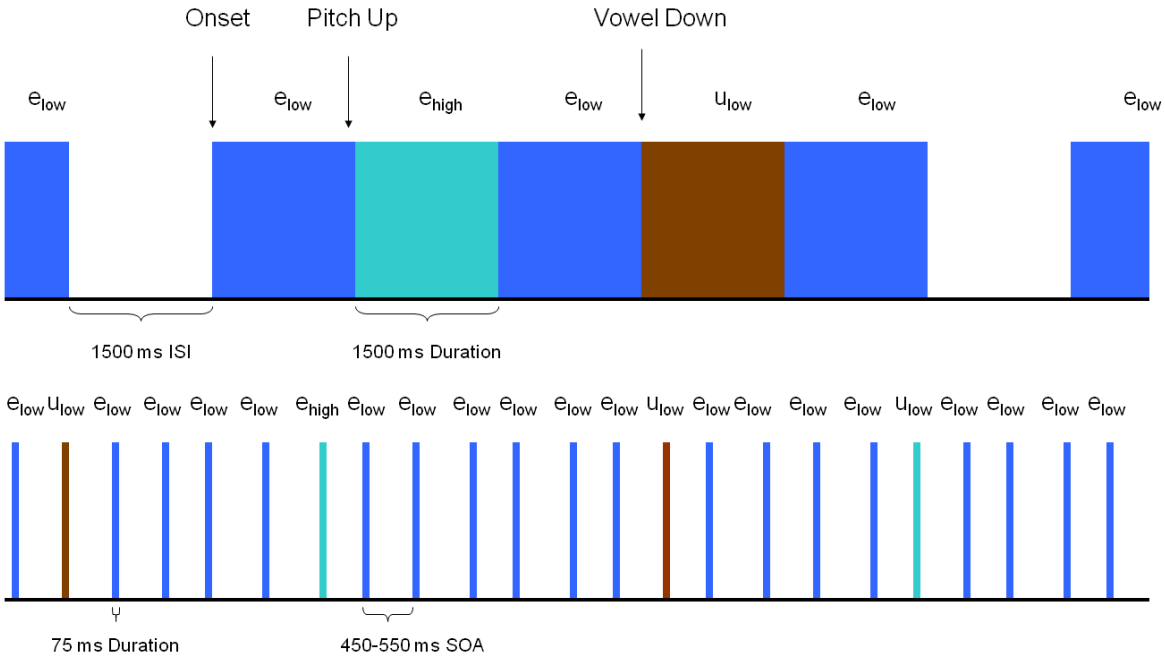

Figure 1. Schematic comparison of the magnetic acoustic change complex (mACC; top) and mismatch field (MMF; bottom) paradigms, both presenting pitch and vowel changes.

MEG recording

To keep participants awake during the recording, they watched a silent subtitled DVD of their choice projected on to the ceiling of the magnetically shielded room. They were asked to ignore the sounds and give their full attention to the movie.

All MEG testing was performed at the KIT-Macquarie Brain Research Laboratory. Neuromagnetic data were recorded using 160-channel whole cortex MEG (Model PQ1160R-N2, KIT, Kanazawa, Japan). The MEG system consists of 160 coaxial first-order gradiometers with a 50 mm baseline (Kado et al., 1999; Uehara et al., 2003). Radial gradiometers detect the maximum signal at points where magnetic flux enters or leaves the scalp.

Prior to MEG recording, five marker coils were placed on an elasticised cap on the participant's head, and their positions and the participant's head shape were measured with a pen digitiser (Polhemus Fastrack, Colchester, VT). Head position was measured with the marker coils before and after each MEG recording with a maximum tolerance for movement of 5 mm. Participants were visually monitored for head movements. The mACC and MMF were acquired in two separate acquisition blocks, each with three blocks of sounds. All sound sequences were presented using Matlab software at 75dB SPL, through G-tubes with eartip inserts (Raicevich, Burwood, Dillon, Johnson, & Crain, 2010). Marker coils were re-measured at the beginning and end of each block to monitor and compare head movements between the blocks.

MEG Data Analysis

Data were sampled at 1000 Hz. Each participant's MEG recording was divided into epochs starting 100 ms before the onset of each stimulus, and ending 600 ms later (i.e., epochs were -100 to 500ms). The BESA Research 5.3 (BESA Research, Grafelfing, Germany) artefact scan tool was used to reject epochs with amplitudes greater than 2700 fT/cm and gradients of 800. This removed trials with abnormally high amplitudes or abrupt

rises or falls in amplitude. Where applicable, bad or flat channels were interpolated in BESA Research. Data were then filtered from 0.1-30 Hz and epochs for all 160 channels were exported as a text file.

For both the mACC and MMF response, the global field power (GFP) was calculated to give an overall measure of scalp field strength (Lehmann & Skrandies, 1980). The GFP was determined at each time sample by first subtracting the average signal across all 160 channels from the signal at each channel, converting all measurements to their absolute values, and then averaging across all sensors. Although it would be possible to analyse the data in source space, by placing dipoles in bilateral auditory cortex, this is likely to underestimate the MMF, which is known to include contributions from outside the auditory cortex. The GFP provides an assumption-free measure of signal strength (Koenig et al., 2011). MEG sensor activity calculated using GFPs has been found to be highly correlated with ECD dipole fitting in terms of strength and latency and is thus is a good estimate of underlying source activity (Kasai et al., 2002, 2003).

To enable a direct comparison of the MMF and mACC, the SNR was calculated for each subject and each condition by averaging the GFP between 30 and 300 ms and dividing by the average GFP in the pre-stimulus baseline (-100 to 0ms) as recommended by Martin (2010). Unlike Martin and Boothroyd (1999), and Martin (2010), who had to calculate noise in SNR in a slightly different way because their stimuli did not include a clear baseline period, our stimuli included 1500 ms silence periods (where there should be no signal), where we were able to calculate the noise from. The 30-300 ms time window was chosen as it included clearly the components of interest in both MACC and MMF (see Figure 2 for grand mean GFP waveforms).

Results

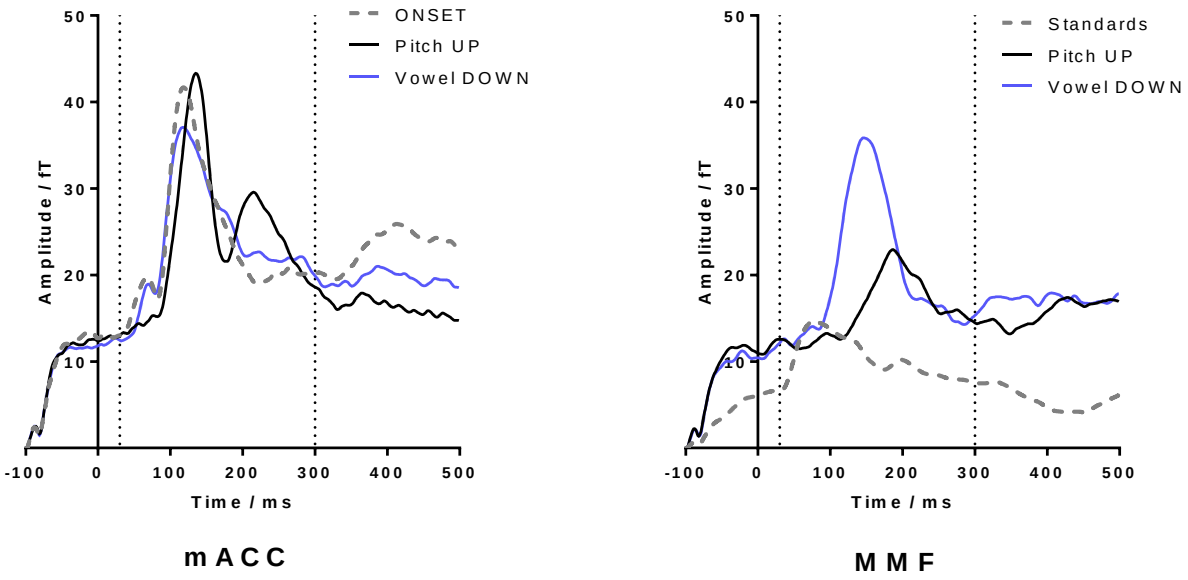

Figure 2. Grand mean global field power (GFP) waveforms for the magnetic acoustic change complex (mACC; left) and mismatch field (MMF) paradigm (right). The mACC paradigm consists of three mACC responses, "onset" (in dotted line), mACC "pitch up" (in black) and mACC "vowel down" (in light blue). The MMF paradigm consists of "standard" responses (dotted grey line), and MMF "pitch up" (in black) and MMF "vowel down" responses (in light blue). MMF "pitch up" and MMF "vowel down" are difference waveforms (subtracted from "standards"). The signal of interest is between 30 – 300 ms, as indicated by the vertical dotted lines.

Grand Mean Waveforms

Figure 2 shows the mean GFPs for the three corresponding conditions in both the mACC and MMF paradigms. In the MMF paradigm, the response to the standard was weak, likely due to the relatively short SOA. The vowel change showed the clearest MMF response. In the mACC, all three responses, onset, pitch up and vowel down, were almost identical in amplitude, with the onset and vowel down being most similar in terms of

morphology.

Figure 3 shows the MMF and mACC responses of individual participants. In terms of identifiability by visual inspection of the 30 to 300 ms time window post-stimulus, seven participants showed absent or questionable MMFs in the pitch up condition. In the MMF vowel down condition, two participants showed absent or questionable MMFs. In the mACC condition, two participants showed absent or questionable responses uniformly for both pitch and vowel change.

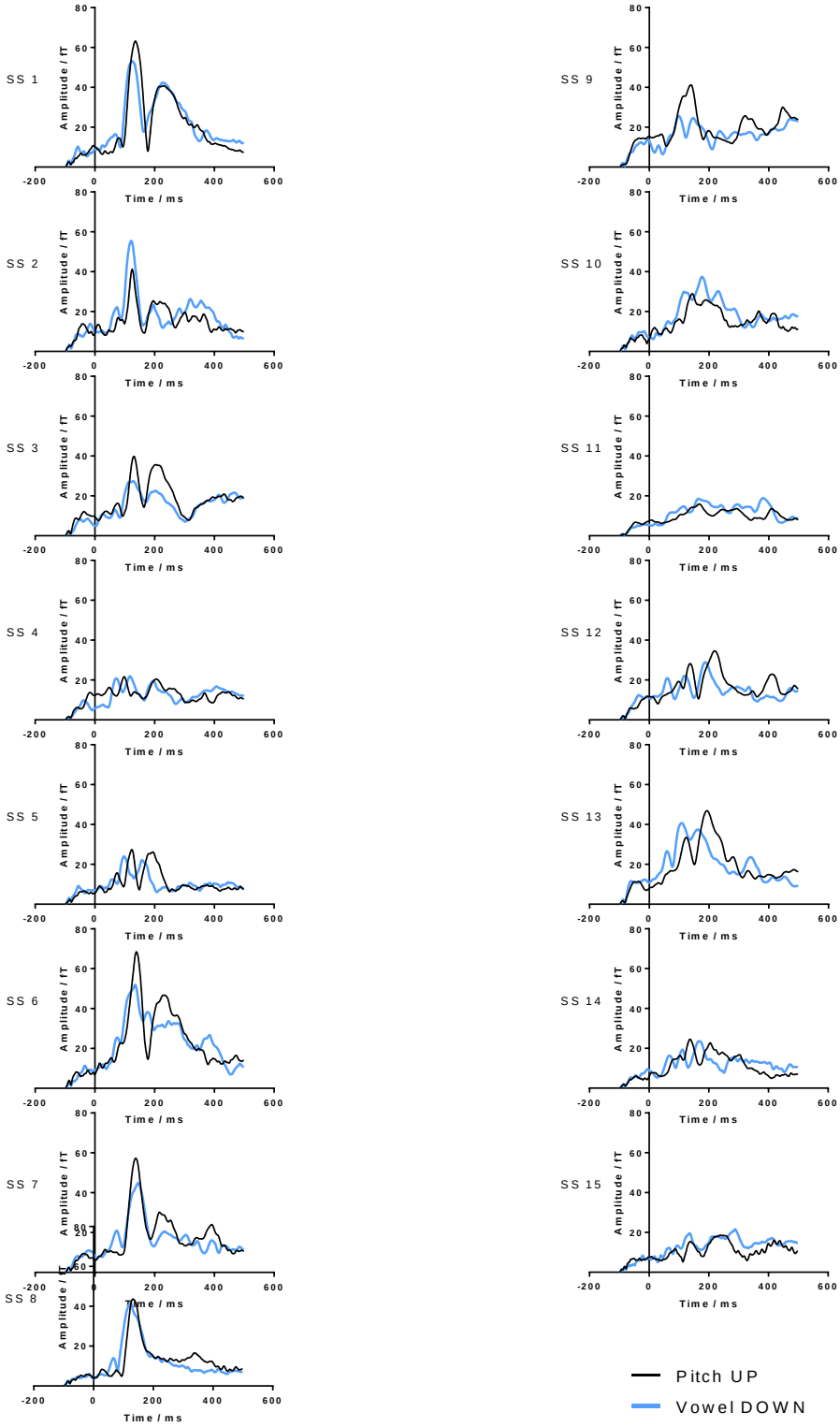

Figure 3. Magnetic acoustic change complex (mACC) global field power (GFP) waveforms from each of the 15 participants for "pitch up" (black line) and "vowel down" (light blue line) mACCs.

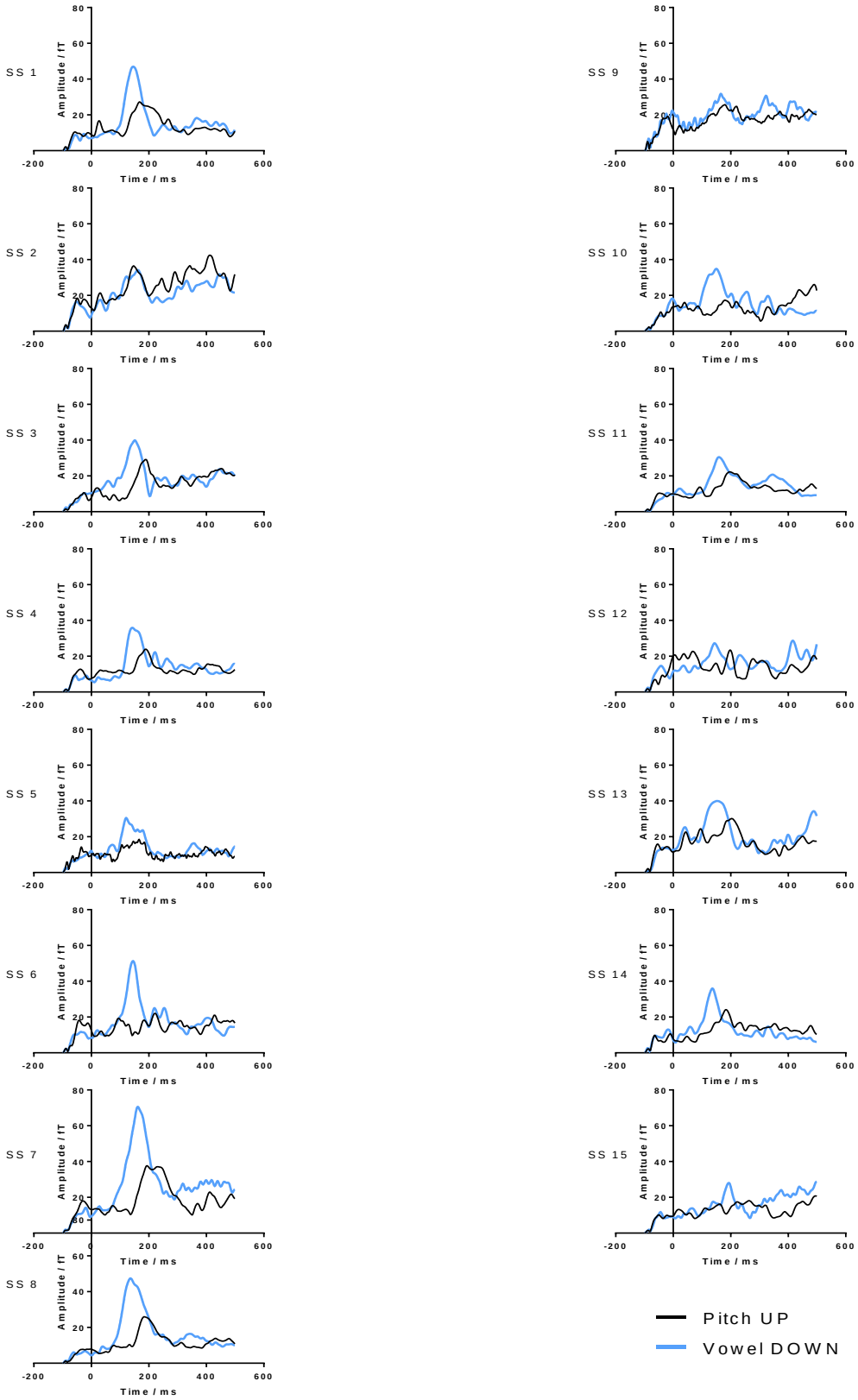

Figure 4. Mismatch field (MMF) global field power difference waveforms from each of the 15 participants for "pitch up" (black line) and "vowel down" (light blue line) MMFs.

Amplitude (Signal)

Averaged grand mean signals across the 30-300 ms window are shown in Table 2. A 2 X 2 ANOVA with "paradigm" and "change type" showed a main effect of paradigm, F (1, 14) = 16.88, $p < 0.01$. That is, the mACC paradigm elicited signals of higher mean amplitude than the MMF. There was also an interaction effect between paradigm and change type, F (1, 14) = 10.18, $p < 0.01$. Within the mACC paradigm, the amplitude for the two changes (vowel and pitch) did not differ from each other t (14) = -1.24, $p > 0.05$, whereas the MMF response had a bigger amplitude for vowel change than pitch change t (14) = 4.46, $p < 0.01$.

Table 2

Comparison of Mean Mismatch Field (MMF) and Magnetic Acoustic Change Complex (mACC) Signal (Average Amplitude Over 30-300ms Time Window), Noise (Average Amplitude -100 – 0 ms Pre-Stimulus), and Signal-to-Noise Ratio (over 30 – 300 ms Time Window).

Paradigm	MMF	mACC	Comparison	
	M (SD)	*M (SD)*	*T*	*p*
Amplitude Signal				
Pitch Up	15.53 (3.62)	24.39 (7.92)	4.57	0.00
Vowel Down	19.31 (4.27)	22.90 (6.45)	2.42	0.03
Noise				
Pitch Up	7.98 (2.04)	8.62 (3.00)	0.84	0.42
Vowel Down	7.41 (1.85)	8.33 (2.00)	2.05	0.06
Signal to Noise Ratio (SNR)				
Pitch Up	1.98 (0.34)	3.00 (1.09)	3.40	0.00
Vowel Down	2.73 (0.82)	2.84 (0.84)	0.52	0.62
All Vowels	-	3.18 (0.89)	2.32	0.04
All Pitch	-	3.30 (1.02)	4.84	0.00

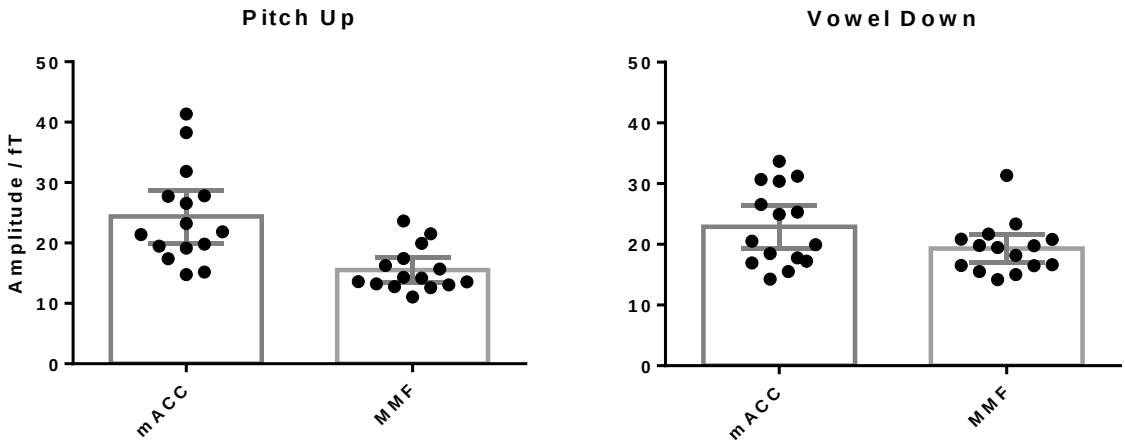

Figure 5. Average global field power (GFP) amplitude (with 95% confidence intervals) for magnetic acoustic change complex (mACC) and mismatch field (MMF) for pitch and vowel changes from 30 to 300 ms.

Noise

Averaged noise in the pre-stimulus -100 to 0 ms window for both paradigms are shown in Table 2. A 2 X 2 ANOVA with paradigm and change type indicates that the two paradigms did not significantly differ in terms of noise levels for both of the change-types (vowel and Pitch), F (1, 14) = 3.58, $p > 0.05$.

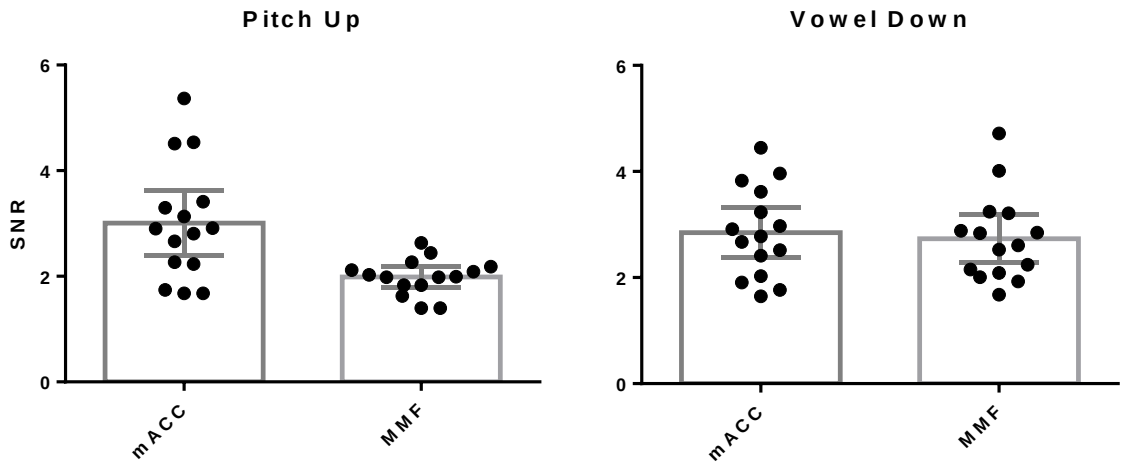

Figure 6. Signal-to-noise ratio (SNR) with 95% confidence intervals for magnetic acoustic change complex (mACC) and mismatch field (MMF) for pitch and vowel changes from 30 to 300 ms.

SNR

Initial analyses compared the two MMFs with the corresponding changes in the mACC (pitch up and vowel down). Averaged SNR across the 30-300 ms window for pitch up and vowel down for both paradigms are shown in Table 2 and Figure 6. A 2 X 2 ANOVA with paradigm and change type showed a main effect of paradigm, F (1, 14) = 9.06, $p < 0.01$, and a main effect of change type F (1, 14) = 4.94, $p < 0.05$. That is, the mACC paradigm elicited higher average SNR than the MMF paradigm, and vowel changes on average elicited higher SNR than pitch changes. There was also an interaction effect between paradigm and change type, F (1, 14) = 5.99, $p < 0.05$. Again, within the mACC paradigm, the SNR for the two changes (vowel and pitch) did not differ from each other t (14) = -0.61, $p > 0.05$. Within the MMF paradigm, the SNR for vowel change was greater than for pitch change t (14) = 4.17, $p < 0.01$. Direct comparison across paradigms revealed that the SNR was greater for mACC than MMF for pitch change but not for vowel change (see Table 2 for mean, standard deviation, t-values and p-values).

Given that the mACC paradigm generated two pitch responses (pitch up and pitch down) and two vowel responses (vowel down and vowel up), we also compared the MMF responses to a combined vowel condition ("all vowels", collapsed prior to the calculation of GFPs) and a combined pitch condition ("all pitch", collapsed prior to the calculation of GFPs). This should theoretically increase SNR by doubling the number of trials and thereby decreasing noise by approximately the square root of two. As seen in Table 2, by collapsing across the two conditions for each change type, there was a main effect of paradigm, with the mACC showing significantly greater SNR than the MMF, F [1,14] = 19.43, $p < 0.01$; and a main effect of change type, F (1, 14) = 5.88, $p < 0.05$. Again, there was also a significant interaction between the paradigm and change type, F (1, 14) = 11.75, $p < 0.01$. Notably, paired t-tests revealed that the mACC had significantly better SNR than for the MMF, both for all pitch, t (4.84), $p < 0.01$, and also for the all vowels, t (14) = 2.32, $p < 0.05$. Thus collapsing across the two directions of acoustic change increases SNR for the mACC.

Efficiency

Efficiency is calculated as SNR divided by total testing time (Martin, 2010). As testing time was 15 minutes in both paradigms, statistical analysis of efficiency gives results identical to those for SNR. The testing time for the MMF was already based on an "optimal" paradigm, but there is considerable scope for improving the efficiency of the mACC. For example, if the aim is to compare the same changes in the mACC and MMF (pitch up and vowel down) then the final e_{low} sound in our mACC stimulus is entirely redundant (see Figure 1).

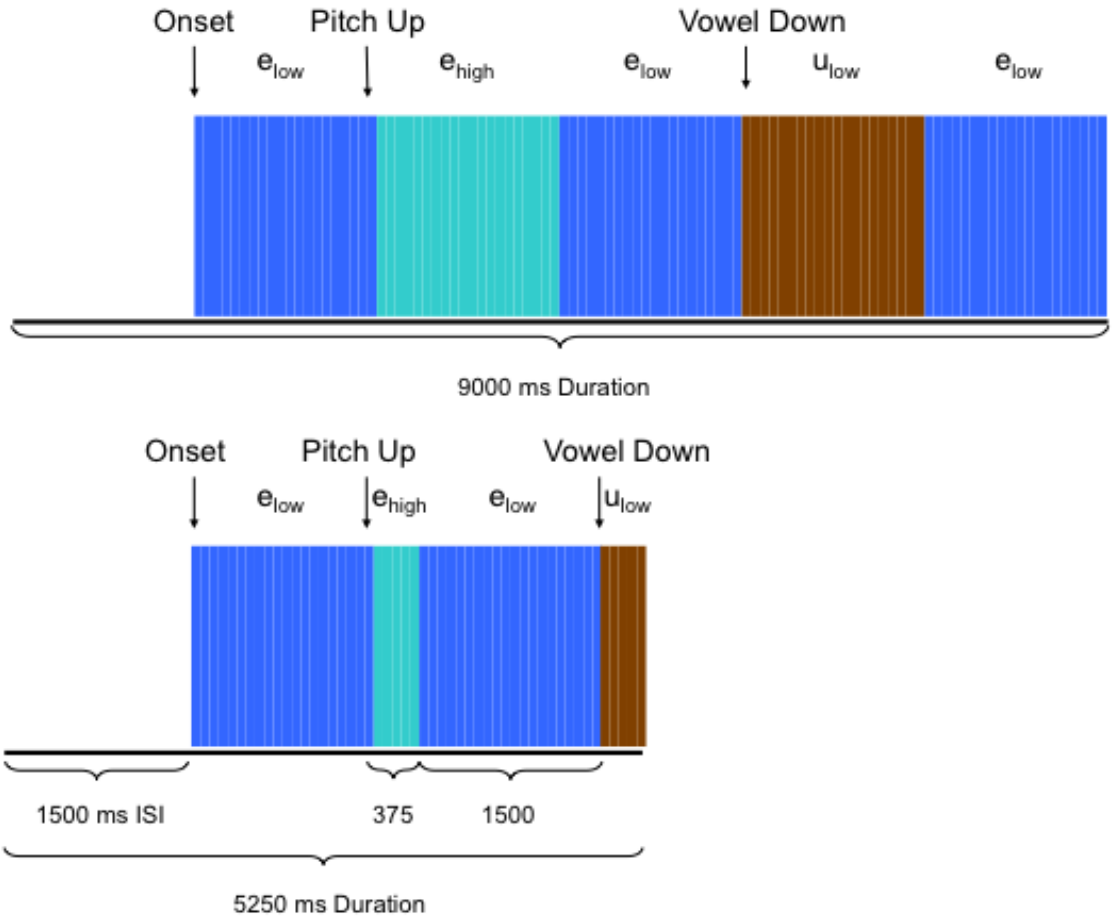

Figure 7. Illustration of the more efficient magnetic acoustic change complex (mACC). The efficiency of the current mACC can be improved upon by shortening the sound change and cutting out the redundant e_{low}.

Efficiency can be further improved by reducing the duration of the mACC stimuli. Each sound within the mACC stimulus was 1.5 seconds, which ensures that the response to the previous transition does not contaminate the response to the current acoustic change. However, given that we are only interested in the first 300 ms after the pitch up and vowel down transitions, it is reasonable to assume that reducing the duration of the sounds following the transitions of interest (post-mACC) would have no impact on the SNR. For example, Figure 7 shows a modified mACC stimulus that allows computation of onset, pitch up and vowel down responses, but each sweep (including ISI) takes 5250 ms rather

than 9000ms. Thus, the same number of sweeps (and the same SNR) can be achieved in 8.75 rather than 15 minutes. Efficiency data for individual participants are shown in Table 3 for the MMF and mACC paradigms tested over 15 minutes, alongside projections for this more optimised mACC paradigm at 8.75 minutes. Note that the optimised mACC is more efficient than the MMF for both changes for all 15 participants.

Table 3

Efficiency Data for Each Participant with Mean and Standard Deviation for the Mismatch Field (MMF) and Magnetic Acoustic Change Complex (mACC) for 15 minutes of Testing Time. A More Efficient mACC ('OptimACC' for short), with 8.75 Minutes Testing Time, is Displayed for Comparison Purposes

Efficiency	MMF		mACC		'OptimACC'	
	Pitch	Vowel	Pitch	Vowel	Pitch	Vowel
SS1	0.15	0.21	0.30	0.26	0.52	0.45
SS2	0.14	0.14	0.15	0.20	0.26	0.34
SS3	0.16	0.22	0.19	0.19	0.33	0.32
SS4	0.12	0.19	0.12	0.14	0.20	0.23
SS5	0.09	0.15	0.21	0.13	0.36	0.22
SS6	0.09	0.19	0.36	0.24	0.61	0.41
SS7	0.14	0.27	0.30	0.16	0.52	0.28
SS8	0.18	0.31	0.23	0.30	0.39	0.51
SS9	0.11	0.11	0.11	0.22	0.19	0.37
SS10	0.12	0.17	0.19	0.26	0.32	0.44
SS11	0.13	0.19	0.18	0.18	0.30	0.31
SS12	0.15	0.13	0.11	0.12	0.19	0.20
SS13	0.13	0.17	0.22	0.17	0.38	0.29
SS14	0.14	0.13	0.19	0.19	0.33	0.33
SS15	0.13	0.14	0.15	0.11	0.25	0.19
Mean	0.13	0.18	0.20	0.19	0.34	0.33
SD	0.02	0.05	0.07	0.05	0.12	0.09

Discussion

The mACC has considerable potential for the investigation of auditory discrimination in clinical populations. Although the MMF has been commonly used for this purpose in previous clinical MEG studies, questions have been raised regarding its reliability and validity as an objective measure of discrimination at the level of the auditory cortex. Here, we found that the mACC was superior to the MMF in terms of the SNR. Moreover, the mACC more consistently elicited responses to both stimuli from individual participants. These findings from MEG are consistent with the EEG work of Martin and Boothroyd (1999) who found that the average amplitude of the ACC was 2.5 times that of the MMN. The superior SNR of the mACC arose because the mACC had a larger signal than MMF, while both paradigms exhibited similar noise levels. The equivalent noise across paradigms reflects a balancing of two opposing factors. On the one hand, there were many more trials in the MMF condition - most consisting of the standard stimuli - contributing to a reduction in noise. On the other hand, the MMF noise is the sum of the noise for the standard stimuli and the much less common deviant stimuli.

The clear differences in SNR arose despite the fact that both paradigms were equated for duration. In principle, the MMF could achieve greater SNR with a longer testing duration. However, time is an essential factor in deciding between auditory discrimination paradigms in clinical and child populations. The aim is for the highest efficiency – the best SNR in the shortest time. Unfortunately, there appears to be little room in the MMF paradigm for increasing efficiency as the chosen procedure was based on what is already considered an "optimal paradigm". In contrast, there are a number of ways of improving efficiency of the mACC. Martin and Boothroyd (2000) achieved this by omitting the silences in between each ACC sequence to create continuously alternating stimuli. This decreased testing time without compromising amplitude of responses in either children or adults. However, this means that no onset response is elicited and it may be

useful in some research aims to have this as a comparison for the mACC (see Martin, 2010 for a discussion on deciding between the continuously alternating ACC or interrupted ACC sequences). As mentioned in the Results, the efficiency of the mACC could be increased by collapsing across similar conditions of interest and/or by shortening the ISIs in the continuous alternation between two sounds. Further increases in efficiency could be made by reducing the duration of the sound *before* each acoustic change of interest. This may lead to overlapping cortical responses, but these could potentially be disentangled using deconvolution techniques (Bardy, McMahon, Yau, & Johnson, in press).

Interestingly, while the mACC responses to pitch and vowel change were similar, at least in terms of amplitude, the MMF was considerably larger for the vowel change than for the pitch change. One possible explanation is that the increased MMF for vowel changes reflects the influence of linguistic long-term memory traces (see Pulvermüller & Shtyrov, 2006 for a review) – something the mACC, which only indexes discrimination of physical difference, is insensitive to. However, we also note that, in our recent study, investigating the mACC response using rapid transitions between stimuli (Bardy et al., 2014), the vowel mACC was larger than the pitch mACC, mirroring the current findings for the MMF. This suggests that the duration between changes in the stimuli may be crucial in determining the mACC paradigm's sensitivity to different acoustic changes.

Overall, our results suggest that the mACC is a better task (higher SNR and efficiency) and better suited to answer questions related to simple change detection than the MMF. However, this is not to say that MMN/MMF should be abandoned. At present, it is not clear how far the ACC paradigm can be extended, especially for more complex stimuli (e.g native-language-relevant stimuli). For example, while the MMN from a typical oddball paradigm involving standard /ba/ sounds interspersed with deviant /da/ sounds informs us about the distinctions between /ba/ and /da/, the ACC would inform us on the change from /a/ to /d/ and /a/ to /b/.

Ultimately, the decision to use the MMF or mACC depends on the question to be answered. The MMN/MMF may provide information on how the brain is making 'intelligent' and abstract representations of complex rules, hence making it useful in studies probing implicit higher order cognitive function (Kujala et al., 2007; Näätänen, 2001; Näätänen, Jacobsen, & Winkler, 2005; Näätänen et al., 2001; Pulvermüller & Shtyrov, 2006). However, if researchers were interested in simply whether or not the brain was sensitive to the differences between two stimuli, the mACC would appear to be the paradigm of choice.

While still under development, the ACC/mACC shows promise for studies with clinical populations such as the hearing or language impaired where behavioural testing of simple acoustic discrimination may be confounded by limits in attention or language. The ACC/mACC also holds considerable promise in studies of child populations. Martin et al. (2010) found that the continuously alternating ACC paradigm elicited high amplitudes in children in a short amount of time. The MMN may be clinically applicable in differential diagnosis of children with learning difficulties into groups with auditory deficits and those with later higher order linguistic processes (Kraus et al., 1996). The ACC/mACC offers the capability to make a further distinction between those with basic auditory discrimination or change detection deficits, and those with higher-order auditory discrimination deficits.

In conclusion, the mACC shows higher SNR and is more efficient than the MMF for the linguistically relevant stimuli tested in this study (pitch and vowel changes). This high SNR extends equally to both types of stimuli, while the MMF was more sensitive to vowel than pitch changes. In addition to SNR, the ACC has its advantages over the MMN, in terms of its test-retest reliability (Tremblay et al., 2003) and correspondence to behavioural measures of acoustic change (Martin, 2007; Martin & Boothroyd, 2000). It also has a simpler interpretation. As Picton et al. (2000) noted, the oddball paradigm which gives rise to the MMN can be adapted to study a multitude of cognitive processes. If

simple auditory discrimination is the focus of the study, the mACC should be used, as it is easy and fast to elicit, its responses are high in SNR, and it is easy to identify.

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Chapter 5

Auditory discrimination in children with autism spectrum disorders: a magnetic acoustic change complex study

Yau, S.H., McArthur, G., & Brock, J. (2014). Auditory discrimination in children with autism spectrum disorders: a magnetic acoustic change complex study.

Abstract

It has been hypothesised that children with autism spectrum disorders (ASD) with impaired spoken language have atypical auditory discrimination. The existing evidence for this hypothesis is mixed, possible due to the questionable reliability of the mismatch negativity (MMN), which has been used by numerous studies to measure auditory discrimination in individuals with ASD. The aim of this study was to use a more reliable measure of auditory discrimination, the magnetic acoustic change complex (mACC), to determine if there is an association between auditory discrimination, reading, and spoken language in 19 school-aged children with ASD and 19 children with typical development (TD). At the group level, children with ASD had significantly smaller mACC responses and significantly poorer spoken language than children with TD. However, the relationship between mACC and spoken language scores was not reliable at the individual level. We offer suggestions for how future studies could better investigate the relationship between mACC responses and spoken language in individuals with ASD.

Keywords: Autism Spectrum Disorder, Auditory discrimination, Acoustic Change Complex, Magnetoencephalography

Auditory Discrimination in Children with Autism Spectrum Disorders: A Magnetic Acoustic Change Complex Study

Introduction

Autism Spectrum Disorder (ASD) is a condition defined in terms of social and communication difficulties co-occurring with repetitive and restricted behaviours (APA, 2000). It has been hypothesised that language impairments observed in many children with ASD may arise from the atypical processing of sounds, and in particular, the ability to discriminate between sounds (Čeponienė et al., 2003; Rapin & Dunn, 2003). Poor auditory discrimination may affect the ability of a person to discriminate between speech sounds, which may interfere with their ability to accurately perceive incoming speech sounds. This in turn might impair their ability to learn the phonology, syntax, and semantics of their native language, hence leaving that person with impaired language (Bishop & McArthur, 2004; Gage, Siegel, Callen, & Roberts, 2003; Oram Cardy, Flagg, Roberts, & Roberts, 2005, 2008).

A particular challenge facing studies investigating auditory discrimination in ASD is that a proportion of individuals with ASD often lack the levels of spoken language ability and attention that are required to produce valid scores on behavioural tests of auditory discrimination (Oram Cardy et al., 2008; Roberts et al., 2008). To address this problem, a number of studies have used the mismatch negativity (MMN) event-related potential (ERP) and the magnetic mismatch field (MMF) event-related field (ERF) to test individuals with ASD for their auditory discrimination. The MMN and MMF are elicited when the brain detects a rare "deviant" sound that is presented amongst many "standard" sounds (Näätänen, Gaillard, & Mäntysalo, 1978). Brain responses to these standard and deviant stimuli can be measured without a person's attention. Thus, the MMN and MMF offer an attractive alternative to behavioural tests for indexing auditory processing in individuals with ASD who are unable to meet the demands of psychoacoustic experiments

(Jeste & Nelson, 2009; Nelson & McCleery, 2008; Roberts et al., 2008).

Despite their great promise, the MMN and MMF responses have produced highly inconsistent findings in studies of auditory discrimination in ASD. While some studies have found typical MMN or MMF responses in individuals with ASD (Čeponienė et al., 2003; Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1995), other studies have found that the MMN or MMF in these individuals is atypically small or absent (Kuhl, Coffey-Corina, Padden, & Dawson, 2005; Tecchio et al., 2003), is unusually large (Ferri et al., 2003; Kujala et al., 2010; Lepistö et al., 2005, 2006), is unusually early (Gomot, Giard, Adrien, Barthelemy, & Bruneau, 2002), or is unusually late (Oram Cardy et al., 2005; Roberts et al., 2011; Seri, Cerquiglini, Pisani, & Curatolo, 1999).

There are at least two potential explanations for the mixed MMN/MMF findings in ASD: the heterogeneous nature of ASD and the uncertain reliability of the MMN and MMF. Regarding the former, individuals with ASD have different combinations of social difficulties, communication difficulties, and repetitive and restricted behaviours. Of these three areas of difficulty, it is communication difficulties generally – and spoken language impairments in particular - that are thought to be most closely associated with poor auditory processing. According to this idea, whether (or not) a study finds evidence for an atypical MMN or MMF response in ASD (i.e., poor auditory processing) should depend on the proportion individuals in the ASD sample who have poor spoken language. However, only a few have considered the relationship between individual differences in their ASD sample's spoken language and their MMN/MMF responses. For example, Roberts et al. (2011) found that children with ASD with comorbid language impairment have delayed MMN responses to both speech and nonspeech sounds, compared to TD children and children with ASD with intact spoken language. In younger children with ASD, Kuhl et al. (2005) found that those who preferred nonspeech to speech sounds had smaller or absent MMN responses than the children with ASD who preferred speech to nonspeech sounds.

These findings support the idea that MMN or MMF studies that include a larger proportion of children with poor language are most likely to find atypical MMN or MMF responses.

A second potential explanation for the mixed MMN and MMF outcomes in individuals in ASD relates to the low test-retest reliability and high intra-subject variability of the MMN and MMF responses (Kurtzberg, Vaughan Jr, Kreuzer, & Fliegler, 1995; Uwer & von Suchodoletz, 2000). Researchers have noted that individuals or groups who fail to show an MMN may nevertheless produce reliable auditory discrimination scores on behavioural tasks using the same stimuli (Dalebout & Fox, 2000, 2001; Kurtzberg et al., 1995; Shafer, Morr, Datta, Kurtzberg, & Schwartz, 2005; Sharma et al., 2006; Tervaniemi, Just, Koelsch, Widmann, & Schröger, 2005; Umbricht et al., 2003; Uwer & von Suchodoletz, 2000). The use of the MMN and MMF as a measure of auditory discrimination in ASD is further limited by mixed opinions on what the MMN and MMF actually measure. A non-exhaustive list includes formation of memory representations, making predictions and adjustments of the auditory environment, and the initiation of attention switching to relevant sounds (Bendixen, Schröger, & Winkler, 2009; Escera, Alho, Schröger, & Winkler, 2000; Garrido, Kilner, Stephan, & Friston, 2009; Näätänen, 2011; Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000; Todd, Myers, Pirillo, & Drysdale, 2010). In addition to these "cognitive" interpretations, some researchers argue that the MMN is a mere product of neural adaptation towards repetitive or irrelevant sounds (Jääskeläinen et al., 2004; May & Tiitinen, 2010).

Given problems with the reliability and theoretical interpretation of the MMN and MMF, the current study investigated auditory discrimination in children with ASD using an alternative paradigm that can also be conducted without an individual's attention. The acoustic change complex (ACC) is a change detection response arising from the activation and deactivation of neural populations within the auditory cortex (Martin, 2010; Martin &

Boothroyd, 1999, 2000). Previous studies have shown the ACC response to be reliable in children as well as adults (He, Grose, & Buchman, 2012; Tremblay, Friesen, Martin, & Wright, 2003) and to correlate well with performance on behavioural tests of auditory discrimination (He et al., 2012; Martin, 2007; Martin & Boothroyd, 2000). In their original study describing the ACC, Martin and Boothroyd (1999) reported that the ACC was 2.5 times larger than the corresponding MMN elicited using the same stimuli. Recently, we extended the ACC paradigm to MEG using linguistically relevant stimuli (see Chapter 4). We found that that the magnetic ACC (mACC) had significantly higher amplitude and signal to noise ratio compared to the MMF.

In the current study, we used the mACC paradigm to investigate the auditory cortical responses of children with ASD to linguistically relevant acoustic changes. The stimuli were semi-synthesized vowel sounds incorporating changes in pitch (fundamental frequency) and vowel identity (first and second formants). We also tested the children with ASD for their general spoken language ability. Given the hypothesised link between atypical auditory discrimination and language difficulties in ASD, we predicted that smaller mACCs would be associated with poorer language scores in the ASD group.

Methods

Participants

Written consent was obtained from all parents of participants, and procedures were approved by the Macquarie University Human Research Ethics Committee. Participating families received monetary compensation, and children were given a small prize and a certificate for taking part in the study.

All participants were aged between five and 13, spoke English as their first language at home and school, and were reported by their parents to have normal range of hearing, which was confirmed using the Otovation Amplitude T3 series audiometer prior to testing. There were no significant differences between ASD and TD groups in terms of age, t (36)

=1.38, p = .18), handedness, t (36) = 0.98, p > 0.05), or gender, t (36) = 0.68, p > 0.05).

Children with ASD (N = 19) were recruited from Autism Spectrum Australia, Macquarie University Special Education Centre, and the Sydney Autism Science research website. All had reports from psychologists or paediatricians confirming ICD-10 or DSM-IV diagnoses of ASD. Those who had been diagnosed more than five years ago were administered the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2002) to confirm a diagnosis of ASD. Additionally, 18 of the 19 children with ASD scored above the Autism cut-off (15) on the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003; see Table 1). Analyses were re-run excluding the one child with a sub-threshold SCQ score but this made no qualitative difference to the results.

Typically developing children (TD; N = 19) were recruited through Neuronauts, an online children's science club, and through community advertisements. To be included in the study, children had to have no known history of brain injury, hearing impairment, developmental disorders or ASD in their family. Additionally, TD children had to be below the cut-off for Autism on the SCQ, and their performance on both language tests (see Standardised Tests below) had to fall in at least the average range for their age (i.e., higher than one standard deviation below the age mean).

Table 1

Participant Characteristics and mACC Amplitudes for Children with Autism Spectrum Disorder (ASD) and Typically Developing (TD) Children. ss = scaled scores with a mean (M) of 10 and standard deviation (SD) of 3.

	ASD group				**TD group**				**t-test**		
	M	***SD***	***Min***	***Max***	***M***	***SD***	***Min***	***Max***	***t***	***df***	***p***
Age (years)	10.19	2.59	5.25	13.33	9.06	2.45	5.67	13.00	1.38	36	.18
Social communication questionnaire (cutoff = 15)	21.79	5.78	10	32	4.94	4.14	0	13	9.94	34	.00
Matrices (ss)	10.79	2.68	5.00	14.00	12.05	3.10	8.00	18.00	1.34	36	.19
Recalling sentences (ss)	8.78	3.28	4.00	15.00	10.53	1.90	7.00	14.00	2.00	35	.05
Nonword repetition (ss)	8.65	2.06	6.00	13.00	10.16	1.86	7.00	15.00	2.31	34	.03
Sensor vowel mACC	0.77	.14	.58	1.10	0.95	.31	.48	1.64	2.36	36	.02
Sensor pitch mACC	0.68	0.21	.44	1.33	0.81	.25	.47	1.43	1.71	36	.01
Source LH vowel mACC (fT)	19.46	12.04	-5.65	47.78	31.44	17.05	-3.06	75.43	2.50	36	.02
Source RH vowel mACC (fT)	13.52	12.27	-6.88	39.97	25.96	20.64	-2.85	69.14	2.26	36	.03
Source LH pitch mACC (fT)	13.35	8.26	-3.75	30.14	22.59	11.94	.07	49.01	2.77	36	.01
Source RH pitch mACC (fT)	8.68	8.87	-7.64	25.39	20.65	15.89	-1.00	60.73	2.86	36	.01

Standardised tests

Children were tested for their nonverbal IQ and for their language abilities after their MEG recording session. Nonverbal IQ was measured using the Matrices subtest of the *Wechsler Intelligence Scale for Children* (Wechsler, 2003). On average, the children with ASD scored slightly lower than the TD children on the nonverbal IQ test. However, their mean score fell right on average (i.e., a scaled score of 10), and the difference between the groups was not statistically significant (see Table 1).

Children's spoken language ability was estimated using the Recalling Sentences subtest of the Clinical Evaluation of Language Fundamentals 4th Edition; (CELF-IV; Semel, Wiig, & Secord, 1987) and the Nonword Repetition subtest of the Children's Test of Phonological Processing (CTOPP; Wagner, Torgesen, & Rashotte, 1999). These two tests are widely used as clinical markers of specific language impairment. In the Recalling Sentences subtest, children were asked to repeated sentences that increased in phonological, syntactic, and semantics complexity across trials. In the Nonword Repetition subtest, children were asked to repeat nonsense words that increased simply in phonological complexity between trials. The mean scores of the ASD group on these two tests were significantly poorer than the TD group, as shown in Table 1.

Stimuli for the mACC

Three semi-synthesised speech vowels, (e_{low}), (e_{high}), and (u_{low}) were generated in Praat (Boersma & Weenink, 2006). Pitch changes involved the (e_{low}) and the (e_{high}), which differed in their fundamental frequencies. Vowel changes between /e_{low}/ and /u_{low}/ involved changes in the second and third formats, while the fundamental frequency was held constant. Table 2 shows the formant frequencies of the three sounds.

Table 2

Formant Frequencies in (Hertz) for the Three Stimuli. Pitch and Vowel Changes from (e_{low}) are Italicised.

	$\mathbf{e_{high}}$	$\mathbf{e_{low}}$	$\mathbf{u_{low}}$
F0	*138*	125	125
F1	280	280	280
F2	2620	2620	*920*
F3	3380	3380	*2200*

Two 7500 ms long mACC sequences were created by concatenating five 1500 ms units of sound. The first mACC sequence (Figure 1, A) comprised the sounds e_{low}, e_{high}, e_{low}, u_{low}, e_{low}. The second mACC sequence (Figure 1, B) reversed the order of the e_{high} and u_{low} sounds (e_{low}, u_{low}, e_{low}, e_{high}, e_{low}). Each sequence was separated by a 1500 ms silence. Thus, each sound sequence resulted in an "onset" response (at the start of each sequence to e_{low}), as well as "pitch up" (from e_{low} to e_{high}), "pitch down" (from e_{high} to e_{low}), "vowel up" (from e_{low} to u_{low}), "vowel down" (from u_{low} to e_{low}) and "offset" responses (at the end of each sequence). The sequences were presented in short blocks. Each block contained 33 mACC sequences. Participants were presented with six blocks, alternating between the first and second mACC sequence, resulting in a total of 198 sequences (990 sounds, 198 silences) for each participant. The order of presentation of the sequences was counterbalanced across participants. TD and ASD groups did not differ in terms of overall number of trials completed t (39) = -0.39, $p > 0.05$.

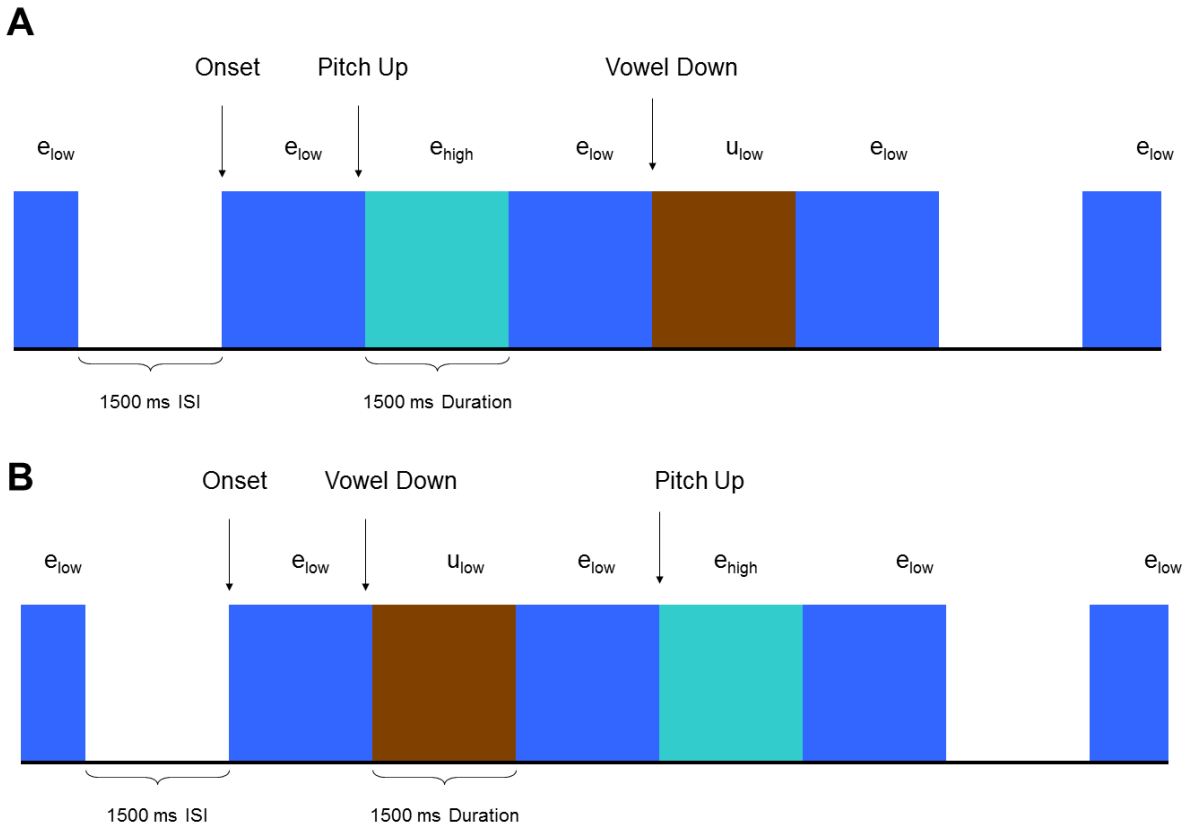

Figure 1. Schematic representation of the magnetic acoustic change complex (mACC) sequences. The top sequence (A) represents the first mACC sequence, and bottom sequence (B) represents the second mACC sequence. Participants heard these two sequences in six counterbalanced blocks.

Magnetoencephalography (MEG) recording

All MEG testing was completed within a one-hour session. Data were recorded using 160-channel whole cortex MEG (Model PQ1160R-N2, KIT, Kanazawa, Japan). The MEG system consisted of 160 coaxial first-order gradiometers with a 50 mm baseline (Kado et al., 1999; Uehara et al., 2003). Radial gradiometers detected the maximum signal at points where magnetic flux enters or leaves the scalp. MEG data were acquired with a sampling rate of 1000 Hz and filter bandpass of 0.03–200 Hz.

Prior to MEG recording, five marker coils were placed on an elasticised cap on the participant's head and the position and shape of the participant's head was measured with a

pen digitiser (Polhemus Fastrack, Colchester, VT). Head position was measured with the marker coils before and after each MEG recording to ensure that each participant's head movement throughout the test session did not exceed 5 mm. Participants were also visually monitored for head movements and reminded to keep still.

The sound sequences were presented binaurally at 75dB SPL, through rubber air-tubes with eartip inserts. During MEG recording, participants watched a silent subtitled DVD of their choice projected on to a screen on the ceiling of the magnetically shielded room. They were asked to ignore the sounds and pay full attention to the movie.

MEG data processing and analysis

The data were analysed at the sensor level and the source level. BESA Research 6.0 (BESA Research, Grafelfing, Germany) was used to process the data. The initial stages of processing the sensor and source analyses were the same. First, the artefact scan tool in BESA was used to exclude trials with amplitudes exceeding 2700 fT/cm or gradients exceeding 800 fT/cm at any one of the 160 sensor channels. The majority of the children (n = 39) had at least 70% artefact-free trials. The two youngest participants with ASD had at least 60% artefact-free trials.

The recording at each of the 160 sensors was epoched from -100 to 500 ms relative to the onset of each mACC stimulus or mACC stimulus change. It was then bandpass filtered from 0.1 (6dB/octave) to 30 Hz (24 dB/octave, zero-phase), and averaged to produce event-related fields (ERFs) to each type of stimulus (onset, pitch up, pitch down, vowel up, vowel down, offset) for each of the 160 sensors. To increase the signal to noise ratio (SNR), the pitch up and pitch down mACC responses were averaged together in BESA (to form "pitch mACC"), as were the vowel up and vowel down (to form "vowel mACC").

Sensor data processing. From this point onwards, the sensor and source data were processed differently. Sensor analysis was conducted on the accepted and averaged onset,

vowel, and pitch mACC epochs. First, sensor data for these three conditions for all 160 channels were exported as a text file into Microsoft Excel. Then, Global Field Power (GFP) was calculated for each response by first subtracting the average signal across all 160 channels from the signal at each channel, converting all measurements to their absolute values, and then averaging across all sensors (Lehmann & Skrandies, 1980; Theuvenet et al., 2011). The GFP provides an assumption-free measure of signal strength (Koenig, Kottlow, Stein, Melie-Garc, 2011; Lehmann & Skrandies, 1980) and provides a good estimate of underlying source activity in MEG (Kasai et al., 2002, 2003). However, a limitation of using the GFP is that the amplitude of responses at the sensors is dependent on the distance between the sensors and the source, which varies naturally as a function of head size. Thus, following Pang (2011), we normalized each participant's pitch mACC and vowel mACC responses by dividing by the amplitude of their own onset mACC response during the 70 – 170 ms window.

Visual inspection of the grand averaged sensor waveforms (see Figure 2) indicated that, across participants, the mACC responses took place within a 70-170 ms window following the change in the stimulus. Thus, this time window was used for all analyses of the pitch mACC and vowel mACC.

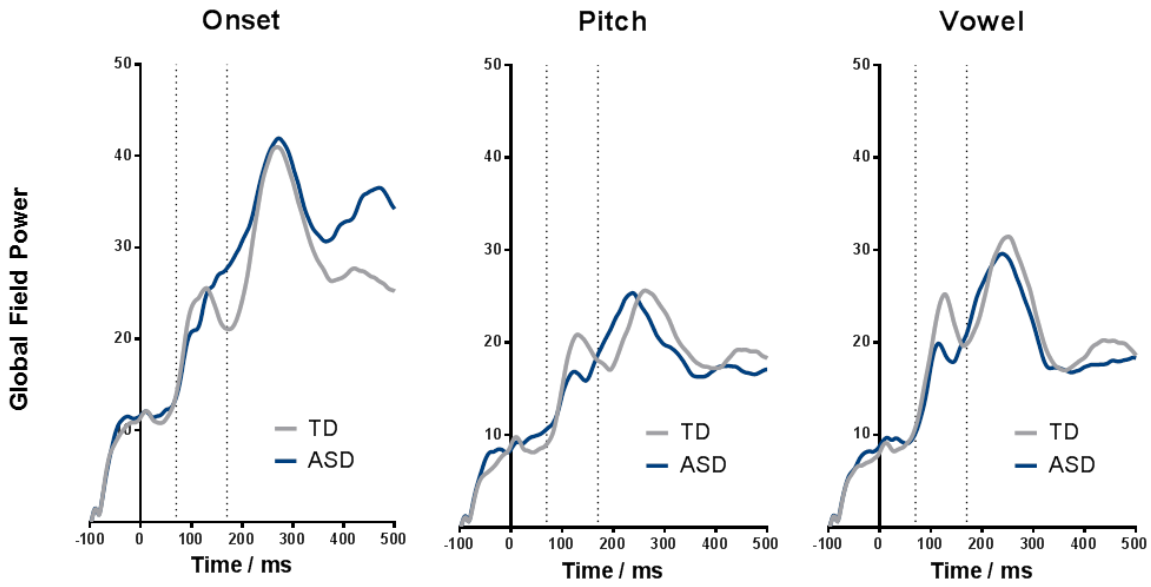

Figure 2. Mean sensor waveforms for the onset, vowel and pitch changes for the children with typical development (TD) and children with autism spectrum disorders (ASD). Vertical dotted lines denote the 70 – 170 ms time window used to calculate magnetic acoustic change complex (mACC) amplitudes.

Sensor data processing. The previously accepted epochs in the sensor data (onset, pitch up, pitch down, vowel up, vowel down, offset) were similarly accepted for the source analysis. To further increase SNR to maximise our ability to find accurate sources in our participants, the two mACC responses were averaged together. Using Classical LORETA Analysis Recursively Applied (CLARA) in BESA 6.0, we identified the focal point for localisation of auditory cortex activity to each mACC condition. CLARA is a distributed source modelling method with additional constraints applied to reach an 'optimum' source solution. Its aim is to make distributed sources more focal by iteratively applying a Low Resolution Electromagnetic Tomography algorithm (Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002). Each iteration reduces the source space to further constrain the possible distribution of sources that model the data so that they are more focal. For each child, we identified the peak in the first principal component of the averaged mACC response

between 70 and 170ms and performed CLARA analysis on a 10-ms window centred on that peak. Dipoles were then placed in the locations of maximum activation (one in each hemisphere) identified by CLARA and then oriented to optimise the fit for that 10ms window. To be included in the source analysis, dipoles for each child identified through CLARA had to satisfy the criteria: (1) the two dipoles must originate from the auditory cortex; and (2) the two dipoles fitted must explain at least 85% of the variance in the 100 (±15 ms) and 130 ms (±20 ms) post-stimulus time window. This time window was determined from the clearest M50/M100 obligatory peak in the group grand average and extended slightly to allow us to capture the variability in responses from younger children or those with maturing waveforms (Oram Cardy et al, 2008).

From here, a pitch mACC and vowel mACC waveform was extracted from the two dipole sources, resulting in left and right hemisphere source waveforms for each condition. Statistical analyses were conducted on the peak amplitudes of the two mACC responses within the 70 – 170ms window, as determined from the grand average data.

Statistical analyses

The sensor data processing stages produced pitch mACC and vowel mACC waveforms in the 70 to 170 ms time window normalised to each child's own onset responses. Left and right hemisphere source waveforms for each child consisted of pitch mACC and vowel mACC localised and extracted from each hemisphere. In the first analysis, the mean sensor pitch mACC and mean sensor vowel mACC in the ASD and TD groups were compared using a 2 x 2 analysis of variance (ANOVA) with condition (pitch mACC and vowel mACC) and group (ASD and TD) as factors. In the second analysis, a 2 x 2 x 2 ANOVA was used to compare condition (pitch mACC and vowel mACC), group (ASD and TD), and hemisphere (left and right). In the third analysis, the pitch mACC and mACC at the sources (left and right hemisphere) were correlated with language in the ASD and TD groups separately. In line with Cohen (1988), r values of 0.1, 0.3, and 0.5 were

considered to be small, moderate, and large (respectively) in effect size. For all analyses, an effect was considered to be statistically significant if $p < 0.05$ unless p was adjusted for multiple comparisons.

Results

Sensor analysis

Figure 3 illustrates the mean mACC responses of the ASD and TD groups at the sensors. Table 1 shows the means, SDs, and range of the sensor mACC scores for the ASD and TD groups for the pitch and vowel changes. A 2 x 2 ANOVA yielded a main effect of condition, $F(1, 36) = 14.88$, $p < .01$, because the average sensor vowel mACC was significantly higher than the average sensor pitch mACC across groups. There was also a significant main effect between groups, $F(1, 36) = 4.89$, p =.03, with ASD participants showing lower average sensor mACCs than children with TD. There was no significant interaction effect. Thus, as can be seen in Figure 3 and Table 2, children with ASD, on average, had smaller sensor pitch mACC and sensor vowel mACC responses than children with TD.

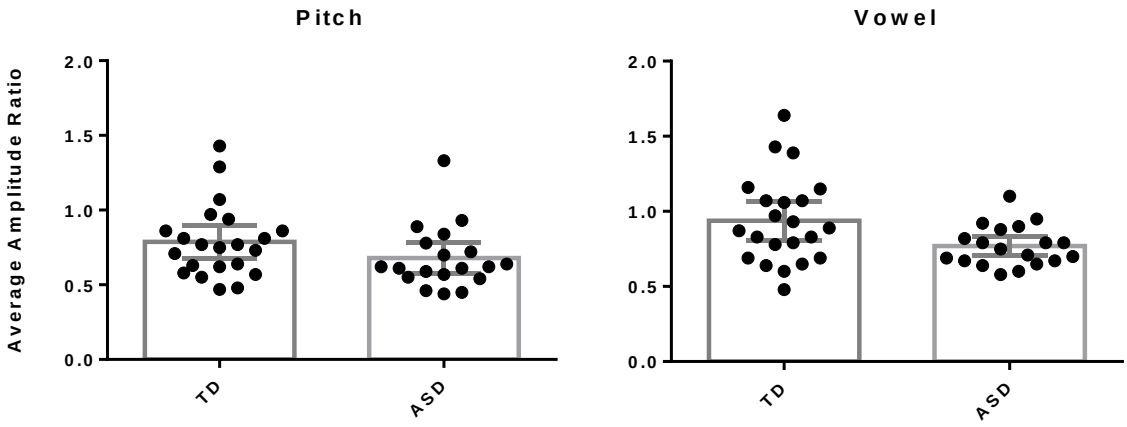

Figure 3. Sensor magnetic Acoustic Change Complex (mACC) scores for the children with typical development (TD) and children with autism spectrum disorders (ASD) for pitch changes (left) and vowel changes (right). Scores reflect the size of each child's pitch mACC and vowel mACC relative to their onset mACC in the 70 – 170 ms time period. Error bars show 95% confidence intervals.

Source analysis

Seven participants (two children with TD and five children with ASD) were excluded from the source analysis because they failed to satisfy the criteria set out in source analysis (see Methods section). Specifically, in these children, we were unable to identify bilateral auditory responses, or fit dipoles to the mACC, suggesting a noisy or absent mACC response identified by CLARA at the source. Figure 4 shows the source waveforms for the remaining 14 children with ASD and 17 children with TD. Table 1 shows the means, SDs, and range of source mACC scores for the ASD and TD groups for the pitch and vowel changes in the left and right hemispheres.

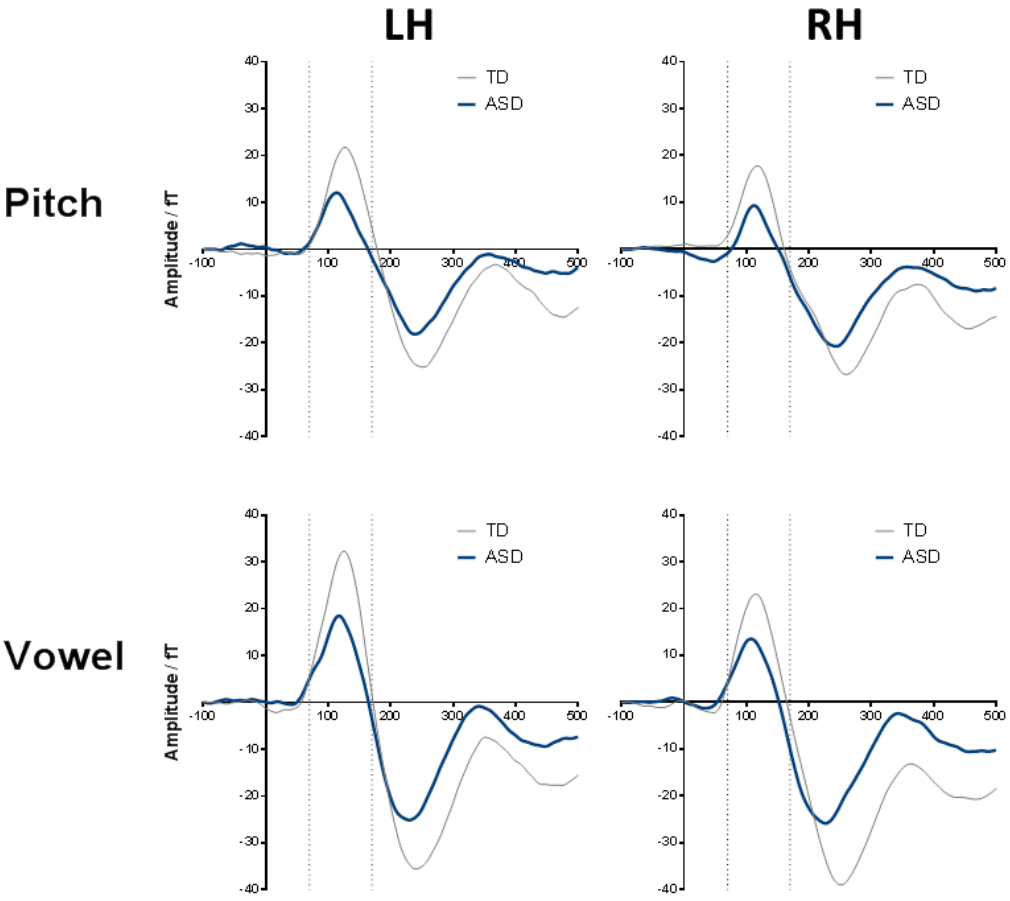

Figure 4. Mean source waveforms for vowel and pitch changes for the children with typical development (TD) and children with autism spectrum disorders (ASD) for left hemisphere (LH) and right hemisphere (RH). Vertical dotted lines denote the 70 – 170 ms time window used to calculate peak magnetic acoustic change complex (mACC) amplitudes.

A 2 x 2 x 2 ANOVA revealed a main effect of condition, F (1, 29) = 24.81, p < 0.01, because the mean source vowel mACC was larger than the mean source pitch mACC. There was also a main effect of group because the ASD group had significantly smaller source mACC responses than the children with TD, F (1, 29) = 8.40, p < 0.01. In addition, there was a main effect of hemisphere, F (1, 29) = 5.53, p = .03, because the mean source mACC in the left hemisphere was larger than the mean source mACC in the right hemisphere. There were no significant interactions between condition, group, and

hemisphere. Thus, the source mACCs were generally reduced in the ASD group in both hemispheres (see Figure 5).

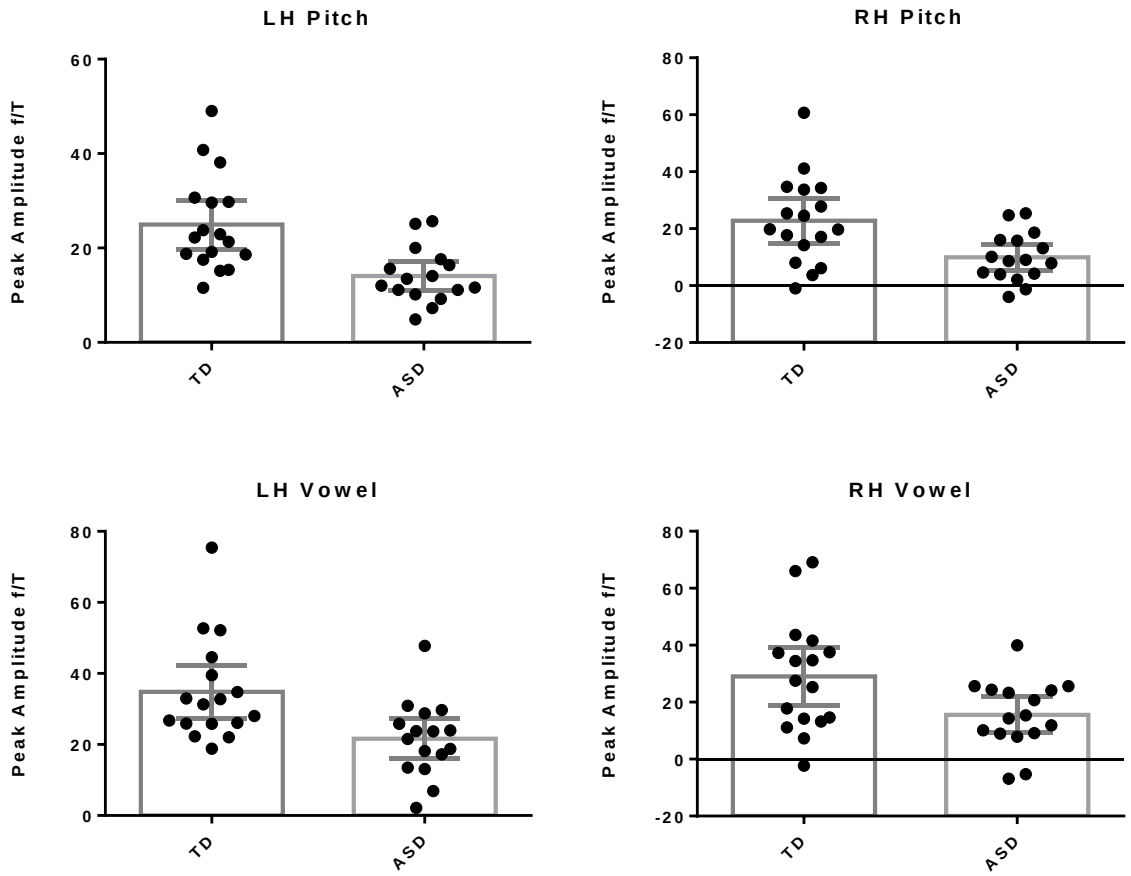

Figure 5. Source magnetic Acoustic Change Complex (mACC) scores for the children with typical development (TD) and children with autism spectrum disorders (ASD) for left hemisphere (LH) pitch changes and right hemisphere (RH) vowel changes. Scores reflect the size of each child's peak amplitude pitch mACC and vowel mACC in the 70 – 170 ms time period. Error bars show 95% confidence intervals.

Correlational analysis

In the ASD group, one child failed to complete the Recalling Sentences test and two children failed to complete the Nonword Repetition test. Thus, these scores were

missing from the correlational analysis for the ASD group. Table 3 illustrates the Pearson r correlation coefficients between each mACC measure and Recalling Sentences and Nonword Repetition scores in the ASD and TD groups separately.

Table 3

Pearson r Correlation Coefficients for Typically Developing (TD) and Autism Spectrum Disorder (ASD) Groups Calculated Between Magnetic Acoustic Change Complex waveforms (MACCs) for Sensor and Source (Left and Right Hemisphere) Waveforms in the 70 - 170 ms Time Windows and Language Scores. No Relationships were Statistically Significant After Correction for Multiple Comparisons (p = .008).

			Sensor mACC		**Source mACC**			
			Pitch	**Vowel**	**LH pitch**	**RH pitch**	**LH vowel**	**RH vowel**
ASD group	**Recalling**	*r*	-.47	-.15	-.07	-.05	-.25	-.34
	sentences	*p*	.05	.55	.82	.86	.42	.25
		N	18	18	13	13	13	13
	Nonword	*r*	.05	.28	.01	.50	.01	.03
	repetition	*p*	.85	.28	.96	.10	.97	.92
		N	17	17	12	12	12	12
TD group	**Recalling**	*r*	-.26	-.26	-.36	-.21	-.45	-.38
	sentences	*p*	.28	.27	.16	.41	.07	.14
		N	19	19	17	17	17	17
	Nonword	*r*	-.23	-.28	-.34	-.50	-.23	-.57
	repetition	*p*	.34	.24	.18	.04	.37	.02
		N	19	19	17	17	17	17

Prior to corrections for multiple comparisons, there was a statistically significant correlation between Recalling Sentences and sensor pitch mACC scores in the ASD group (r = -.47, p = .05). In addition, in the TD group, there were significant correlations between Nonword Repetition scores and the right hemisphere source mACC for both pitch (r = -.50, p = 0.04) and vowel (r = -.57, p = .02). However, these correlations did not withstand corrections for multiple comparisons (i.e., p would need to be lower than 0.008 to correct for six correlation coefficients within each group for each language score), and were in the opposite direction to what would be predicted by the group comparisons (i.e., poorer mACC scores were associated with better language scores rather than poorer language scores). Thus, we could not rule out the possibility that these correlations between mACC and language scores occurred due to chance.

Discussion

This study is the first to use the mACC paradigm to study auditory discrimination in children with ASD. We used the mACC because it is a stable and reliable response both in adults (Tremblay et al., 2003) and in children (Martin et al., 2010), its amplitude corresponds with auditory discrimination tasks (He et al., 2012), and its higher amplitude and SNR compared to the MMF response (Martin & Boothroyd, 1999; Study 3 in Chapter 4). Our results indicate that mACC responses were significantly weaker on average in the ASD group than TD children. Although there were significant effects of hemisphere and condition, these effects did not interact with group membership, indicating a general reduction in the mACC response to both the pitch and vowel changes used in this study. Importantly, the same group differences were found for sensor and source analyses, suggesting that they were not a consequence of the particular choices made during analysis.

Our findings would appear to contradict previous reports of an enhanced MMN in studies of ASD (Ferri et al., 2003; Korpilahti et al., 2007; Kujala et al., 2010; Lepistö et al.,

2005; Lepistö, Nieminen-von Wendt, von Wendt, Näätänen, & Kujala, 2007; Lepistö et al., 2006). However, as noted earlier, the MMN/MMF has questionable reliability and there are many other studies that have either failed to find an enhanced MMN/MMF in ASD (Čeponienė et al., 2003; Kemner et al., 1995; Gomot et al., 2002; Oram Cardy et al., 2005; Roberts et al., 2011; Seri et al., 1999), or have found a reduced MMN/MMF (Kuhl et al., 2005; Tecchio et al., 2003). Moreover, as mentioned in the Introduction, it has not yet been established what the MMN or MMF responses represent. Differences in the amplitude of the MMN/MMF could reflect differences in memory representations, predictions about the auditory environment, attention towards relevant sounds, or poor neural adaptation towards repetitive or irrelevant sounds. In contrast, the mACC is interpreted uncontroversially as a change detection response arising from the activation and deactivation of neural populations within the auditory cortex (Martin et al., 2010; Martin & Boothroyd, 1999, 2000). The current results would, therefore, appear to provide evidence that changes in auditory stimulation result in a smaller population of neurons becoming activated and deactivated in the brains of children with ASD relative to TD children.

As well as having smaller mean mACC responses, children with ASD had poorer mean language scores than children with TD. While this suggests some degree of association between poor auditory discrimination and poor spoken language, mACC amplitudes were not reliably associated with language scores within the ASD group or the TD group. This combination of findings could be interpreted in at least three ways. The first two relate to the small sample size in this study, which is a limitation when conducting correlational analyses. First, it is possible that the association between the mACC and spoken language is not strong enough to be detected reliably at the individual level, at least without a much larger sample size. Second, it is possible that the ASD sample that we recruited for this study was too homogeneous for testing the relationship between mACC and language scores. Specifically, while the ASD group in this study had poorer spoken

language scores than the TD group overall, there were few children in the ASD group who had scores that fell below the average range (i.e., lower than -1 SD). If the ASD sample had included more children with more severe language problems, we may have found a reliable association between poor mACC scores and poor spoken language scores at the individual level. A third possibility is that the relatively low-level auditory discrimination mechanisms tapped by the mACC are genuinely unrelated to language capabilities. We plan to test these alternative possibilities in future studies.

In conclusion, this study found weaker auditory discrimination in children with autism as indexed by the amplitude of the mACC response. In doing so, this study demonstrated the potential of the ACC paradigm for exploring auditory processing and its neural correlates in ASD and other clinical populations. The ACC complements the widely used MMN paradigm and may be a more clinically useful tool in research where the question pertains specifically to auditory discrimination.

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Chapter 6

General Discussion

GENERAL DISCUSSION

The general aim of this thesis was to investigate the relationship between auditory processing and spoken language in children with autism spectrum disorders (ASD). To this end, the aim of Study 1 was to examine the relationship between spoken language ability and obligatory magnetic source and sensor event-related field (ERF) responses to speech and nonspeech sounds in children with ASD. The aim of Study 2 was to do the same in a nonverbal child with ASD who had no measurable spoken language ability. The aim of Study 3 was to develop a more efficient and reliable measure of auditory discrimination for use in clinical and child populations. Finally, the aim of Study 4 was to use this new auditory discrimination measure to examine the association between auditory discrimination and spoken language in children with ASD. Outlined below is a summary of the findings of each study, followed by the practical and theoretical implications of this research program. This dissertation concludes by considering the potential limitations of the current series of studies, and suggested directions for future research.

Summary of Studies

Paper 1: The relationship between spoken language and speech and nonspeech processing in children with autism: an event-related field study

The aim of Study 1 was to investigate the relationship between the neural processing of speech and nonspeech sounds and spoken language within a typically heterogeneous sample of children with ASD. To achieve this aim, we intended to conduct a mismatch field (MMF) study to look at discrimination of speech and nonspeech sounds. However, we discovered that MMFs could not be reliably elicited in half of the children in both ASD and TD groups. Thus, we focused our analysis on the reliable and robust obligatory magnetic ERF responses (M50-M100) to the standard speech and nonspeech stimuli presented within the MMF paradigm. Using intraclass-correlations (ICCs), we measured how similar each child's sensor ERFs to speech and nonspeech sounds were to

the corresponding mean sensor ERFs for children with typical development (TD). We also used ICCs to measure how similar each child's sensor and source ERFs to speech sounds were to their sensor and source ERFs to nonspeech sounds. We then measured the strength of the relationship between these neural auditory processing measures and spoken language ability within the ASD and TD groups separately. We discovered that children with ASD with poorer spoken language had more impaired auditory processing between 200 and 400 ms in the left hemisphere.

Close inspection of children's left hemisphere brain responses in the 200-400 ms time period suggested that atypical auditory brain responses in children with ASD may represent a general maturational delay. There is evidence that ERFs falling in the 200-400 ms time window may be involved in evaluating a sound's meaningfulness, relevance, or 'speechness' (Čeponiene, Alku, Westerfield, Torki, & Townsend, 2005; Čeponienė, Torki, Alku, Koyama, & Townsend, 2008; Paulmann & Kotz, 2008a, 2008b; Picton, 1992). This evidence suggests that children with ASD with poorer spoken language may have an immature auditory processing system that fails to recognise the salience of speech over nonspeech. Infants at high risk for ASD and young children with ASD have been found to show social orienting deficits towards 'motherese' and speech sounds (Curtin & Vouloumanos, 2013; Klin, 1991, 2003; Kuhl, Coffey-Corina, Padden, & Dawson, 2005). A social orienting deficit has also been suggested in event-related potential (ERP) studies, where the P3a component (around 300 ms) in children with ASD is intact in response to nonspeech sounds but weak in response to speech sounds (Čeponienė et al., 2003; Lepistö et al., 2005). Thus, the outcomes of Study 1, in combination with previous studies, suggest that some children with ASD may have an immature auditory processing system that impairs the preferential bias of speech over nonspeech that supports typical language acquisition (Conboy, Rivera-Gaxiola, Klarman, Aksoylu, & Kuhl, 2005; Vouloumanos & Werker, 2007). This may interfere with a child's acquisition of the phonology, syntax, and

semantics of their native language, leaving them with language impairment.

Study 2: Neuromagnetic responses to speech and nonspeech sounds in a minimally verbal child with autism

According to Tager-Flusberg and Kasari (2013), nothing is known about why some children with ASD do not speak. It has been suggested that this may stem from impaired auditory processing skills (Gage et al., 2011). However, no studies have been conducted to specifically address this hypothesis. In Study 2, we tested GM, a girl with ASD who does not have spoken language, using magnetic ERFs to speech and nonspeech sounds. The similarity of her ERFs to speech and nonspeech sounds were atypically disparate in the 65–165 ms (M50/M100) time window. Specifically, while her brain responses in the left hemisphere were unusually early and strong, her speech responses were much weaker and nearly absent. This pattern was very different from typically developing children and verbal children with ASD, and only occurred in less than 5% of the comparison population.

Two years later, we retested GM for her brain responses to sounds, this time using electroencephalography (EEG) to measure her event-related potentials (ERPs) to nonspeech sounds (tones). The ERPs replicated the ERFs in showing that GM had unusually early and strong brain responses to nonspeech sounds compared to children with TD and verbal children with ASD. The reliability of GM's atypical brain responses to sounds suggests that minimally verbal children with ASD may have an auditory processing deficit characterized by highly contrasting brain responses to speech and nonspeech sounds. If this apparently reliable finding is replicated in other children with ASD who are also nonverbal, then it would support the hypothesis that the more profoundly impaired children with ASD without functional spoken language have a bottom-up sensory encoding of acoustic information that may account for their severe spoken language impairment (Gage et al., 2011; Whitehouse & Bishop, 2008).

Study 3: The magnetic acoustic change complex – a more robust and efficient neural measure of auditory discrimination?

The aim of Study 3 was to develop a new auditory discrimination paradigm for use with children and clinical populations. There are concerns with the current 'gold standard' neural index of auditory discrimination, the mismatch negativity (MMN), with regards to its reliability and stability in children and clinical populations, its poor correspondence with behavioural tests (Bishop, 2007), and the multiple interpretations surrounding its generation (Martin & Boothroyd, 1999; May & Tiitinen, 2010; Näätänen, 2011; Näätänen, Astikainen, Ruusuvirta, & Huotilainen, 2010; Yau et al., 2014, Chapter 3). A new test of auditory discrimination for clinical child populations would need to elicit robust responses within a short period of testing time, have a good signal-to-noise ration (SNR), and would have to be clearly interpretable. The acoustic change complex (ACC; Martin & Boothroyd, 1999), a paradigm that elicits a group of obligatory responses to a change within a sound, has these properties. Hence, in Study 3, we developed a magnetic version of the ACC (the mACC), and compared it to an optimal MMF paradigm (Näätänen, Pakarinen, Rinne, & Takegata, 2004).

We found that the SNR for the mACC was higher than for the mismatch field (MMF), which is consistent with Martin and Boothroyd's (1999) finding of a superior SNR for the ACC over the MMN. It is interesting to note that Martin and Boothroyd reported that the mACC SNR was 2.5 times higher than the MMN, while we found the mACC SNR was 1.18 (for pitch changes) and 1.5 (for vowel changes) times higher than the MMN. This can be explained in terms of the differences in the stimuli used. While we used semi-synthesized speech for both pitch and vowel changes, Martin and Boothroyd used a tonal complex and noise. In addition, these authors noted that their findings applied only to the 'extreme periodicity change used'.

It is also interesting to note that we found a significant interaction between

paradigms (mACC versus MMF) and types of change (pitch versus vowel), with the mACC eliciting similarly high SNRs for both pitch and vowel changes, while the MMF elicited a significantly higher SNR to vowel than pitch changes. The MMF outcome could reflect the different magnitude of change present in the pitch and vowel mACC (i.e., two change parameters for vowel, one change parameter for pitch). This suggests that pre-linguistic memory traces may affect MMF generators differentially (Pulvermüller & Shtyrov, 2006), making changes in vowel identity more salient than pitch changes. In contrast, the mACC may simply reflect a change detection response that is uniform between pitch and vowel changes.

Lastly, and for practical reasons, perhaps most importantly, we found that the mACC was a more time-efficient measure than the MMF. We also identified ways that the efficiency of the mACC could be improved in future studies. In summary, the mACC's respectable SNR, easy interpretation, and time-efficiency support its use as an effective and reliable tool for measuring auditory discrimination in child and clinical populations.

Paper 4: Auditory discrimination and language impairment in children with Autism Spectrum Disorders: a magnetic acoustic change complex (mACC) study

The aim of the fourth and final study was to combined the strengths of Study 1 (i.e., measuring ERFs at both the sensor and source level, and using both within- and between-subjects methods to measure the integrity of brain responses) and of Study 3 (the development of the mACC) to examine the association between auditory discrimination and language impairment in ASD. We found that children with ASD on average had poorer mACC scores than TD children and poorer spoken language scores than TD children. In line with previous studies, this finding supports the idea that children with ASD have impaired auditory discrimination (Oram Cardy, Flagg, Roberts, & Roberts, 2005; Tecchio et al., 2003), and that impaired auditory discrimination may be associated with poor spoken language (Kuhl et al., 2005; Kujala, 2007; Tager-Flusberg, Edelson, &

Luyster, 2011). However, it is important to note that an association was not seen at the individual level. Specifically, the relationship between mACC scores and language scores with the ASD group was not statistically reliable. This might be explained by the restricted range of language scores in the ASD group, which may have underestimated the true strength of a relationship between two variables. Alternatively, it may be the case that the mACC generated by pitch and vowel changes is only weakly associated with language, and so this association is only detected at a group level. It is possible that "prosodic" changes in speech, such as shifts in loudness, rate, or rhythm, may be more closely related to language in ASD since prosodic impairment has been found to be correlated with expressive and receptive language in ASD (McCann & Peppé, 2003; McCann, Peppé, Gibbon, O'Hare, & Rutherford, 2007). We plan to test these alternative possibilities in future studies.

Theoretical Implications

Considered simultaneously, the outcomes of the four studies summarised above offer several theoretical insights into the nature of ASD. In Study 4, using the mACC paradigm, we found evidence for impaired auditory discrimination in ASD. The amplitude of the mACC response was significantly smaller for children with ASD compared with typically developing control participants. However, we failed to find a reliable association between mACC scores and the measures of language ability. These findings are in direct contrast to the earlier findings in Study 1, where we used ICCs to determine how similar the auditory brain responses of children with ASD were to those of TD children. Although we found no significant group differences (i.e., there was no difference between the ASD and TD groups on average), there was a strong association between auditory brain responses to speech and nonspeech sounds and spoken language within the ASD group.

How do we reconcile these two apparently contradictory sets of findings? As always in ASD research, we have to consider the fact that different participants were

involved in the two studies. Given the heterogeneity within ASD, inconsistent findings should almost be expected, and the ability to unearth subgroups could be hindered by our relatively small sample sizes. There were also differences in the stimuli and paradigms. While Study 1 investigated the response to the onset of short vowel sounds and complex tones, Study 4 investigated the response to changes (auditory discrimination) within a continuous vowel sound. In addition, the way we analysed the data was also quite different across the two studies. Our analysis of the mACC responses in Paper 4 focused on the peak amplitude approximately 100 ms after the acoustic change. In contrast, in Paper 1, we determined that the association with language scores was driven primarily by individual differences in the later part of the waveform between 200 and 400 ms after onset.

One possible interpretation of our data, then, is that there are two separate effects in play. First, as found in Paper 4, the relatively early stages of auditory discrimination (around 100 ms) are affected in at least some participants with ASD, but this is independent of their language skills. Second, as found in Study 1 and 2, the later stages of auditory processing (200-400 ms) are affected amongst the subgroup of children with ASD who have language difficulties. Clearly, this theoretical interpretation is speculative, but it does provide clear and testable predictions for future studies.

A second theoretical insight provided by this research program relates to the specificity of atypical auditory brain responses to speech and nonspeech sounds in ASD. Study 4 is silent on this issue because we employed only speech-like stimuli (although we found similar results for pitch and vowel changes within our vowel-like stimuli). In Study 1, we found similar results for speech and nonspeech stimuli. In both cases, the similarity of brain responses to speech and nonspeech (measured using ICCs) were associated with language ability. However, in Study 2, the most striking finding was the clear dissociation in responses to speech and nonspeech sounds of GM, our nonverbal child. Although GM is only a single case, this suggests that there may be some individuals on the autism spectrum

whose brains respond quite differently to speech and nonspeech sounds. As noted in the Discussion of Study 2, the fact that GM's responses were atypical within the first 100 ms or so after onset implicates the early "bottom up" perceptual encoding stages of auditory processing, rather than higher order auditory mechanisms or "top down" attention that would be reflected in later components.

Finally, considered en masse, studies 1, 2 and 4 highlight the complexities and challenges of studying ASD, particularly with regard to the heterogeneity within the ASD population. We are unable to make any clear generalisations about auditory processing in ASD per se. Nonetheless, our findings suggest that individual variation within ASD, particularly in relation to language ability, may be understood in terms of atypicalities occurring at various stages of the auditory processing hierarchy.

Practical Implications

In the course of this research program, we encountered several unanticipated challenges that prompted a number of novel practical solutions. Below are two key practical advances that were made in this research program examining auditory processing in children with ASD.

Complementing source ERFs with sensor ERFs

A particularly difficult challenge that affected three studies in this research program arose from the difficulty of fitting dipoles to measure children's auditory ERFs at the sensors. With adult data, it is relatively straightforward to fit dipoles so that all participants have consistent waveforms (e.g., setting the M50 to always be positive and the M100 negative). However, due to the variability in the timing and the amplitude of children's M50 and M100 responses, it is often difficult to determine the direction of a source waveform. This problem prevented us from creating mean average source ERFs across TD participants. This in turn meant that we could not measure the extent to which each child's source ERFs to speech and nonspeech ERF were typical for their age (i.e., in comparison

to the group mean source ERF for the TD group). However, we were able to use ICCs to index the similarity of each child's nonspeech source ERF to their own speech source ERF (i.e., their speech-nonspeech ICC) because both ERFs were optimised in exactly the same way for both conditions.

Given the limitations of the source ERFs, we turned to MEG data measured at the sensors. Specifically, in studies 1, 2, and 4, we used Global Field Power (GFP) to calculate ERFs to speech and nonspeech stimuli. The GFP provides an assumption-free measure of signal strength (Koenig et al., 2011; Lehmann & Skrandies, 1980), and is a good estimate of underlying source activity in MEG (Kasai et al., 2005; Kasai et al., 2002, 2003). Importantly, GFP allowed us to average the sensor ERFs of children with TD to produce grand mean sensor ERFs to speech and nonspeech sounds. This in turn allowed us to objectively determine how typical each child's sensor speech and nonspeech ERFs were relative to the TD group, which could not be done for source ERFs.

While sensor ERFs can act as a good complement to source ERFs, they are not without their own limitations. On average, children's heads are 10% smaller than adults, for whom most MEG systems are built to fit (Gaillard, Grandin, & Xu, 2001; Pang, 2011). Because magnetic signal strength falls off with the square of the distance from the sensors, ERFs measured at the sensors are smaller in children than adults, which affect the SNR of children's sensor responses. Thus it was necessary to incorporate an appropriate control in sensor analysis. Fortunately, this was exactly the same control as we used for the source ERFs. Specifically, we used ICCs to index the similarity of each child's nonspeech source ERF to their own speech source ERF (i.e., their speech-nonspeech ICC) since each child acted their own control in terms of head size, shape and distance from the sensors.

In summary, measuring both source and sensor ERFs in children have their unique challenges and limitations. From our experience in this research program, we would recommend that when measuring auditory ERFs in children, researchers should (1)

measure both source and sensor ERFs (rather than just source ERFs), (2) use GFPs for sensor analyses, and (3) use ICCs (or an equivalent) to conduct within-subjects comparisons to control for problems associated with fitting dipoles (for source ERFs) and differences in head size (for sensor ERFs).

The mACC

Another practical outcome of this research program is the development of the mACC. Previous studies have found that the ACC is a reliable response (Tremblay, Friesen, Martin, & Wright, 2003) that correlates with behavioural measures of acoustic change (Martin, 2007; Martin & Boothroyd, 2000). The outcomes of Study 3 suggest that the magnetic ACC (the mACC) may be a particularly useful measure of neural auditory discrimination in children or special populations for three main reasons. First, it has a superior SNR to the current gold standard measure – the MMN. Second, mACC responses are relatively easy to interpret since they simply reflect the activation and deactivation of neurons in the auditory cortex. Third, the mACC is a more time-efficient measure compared to the MMF, which means it has very useful applications for testing less co-operative child and clinical populations. The efficiency of the mACC could be further increased by collapsing across conditions with similar changes, slightly shortening the time of the stimulus after the change of interest has occurred, or by using a more efficient ACC paradigm that omits the silences in between to produce a continuously alternating ACC (Martin, Boothroyd, Ali, & Leach-Berth, 2010). Thus, we suggest that future studies of auditory discrimination use the mACC to further understand which level of auditory discrimination is impaired in ASD. Even better, future studies might use both mACC and MMF paradigms to see if individuals with ASD who were missing an MMN/MMF to be also missing the mACC. This would increase our understanding about the differences between auditory processing of a basic change detection response in ASD and a higher level regularity-violation response.

Limitations and Future Research

Assessing the auditory processing abilities of verbal and minimally verbal children with ASD is not easy. The studies in this thesis faced a number of challenges. While some of these were conquerable (see above), others imposed limitations on the execution of a study or interpretation of the outcomes. Outlined below are five limitations that affected the studies in this research program, along with suggestions for how studies might address these limitations in the future.

Difficulties with MEG sensor and source analyses in children

Our research is not the first to raise issues on source localisation in neurophysiological research, especially in children (Pang, 2003, 2011; Webb et al., 2013). These issues pertain to calculating individual source waveforms that are representative of the control group, which could be affected by individual differences as well as individual variation in head movement. While these issues are relevant, it is noteworthy that we circumvented some of the major confounds in individual differences by using a within-subjects paradigm. For individual head movement, we imposed strict criteria for inclusion in every study that excluded children whose heads were more than 5mm away from where they started out in the MEG helmet. We also combined the complementary strengths of sensor and source analyses: While activity at the sensors can be affected by the distance between a child's head and the MEG helmet (bigger auditory responses could be a true representation of the strength of responses, or a product of a larger head and/or closeness to the helmet), activity from the sources is dependent on the source analysis algorithm and head model fit. Hence, a feasible alternative is to measure ERFs at the sensors, as we have done in studies 1, 2 and 4, using GFP, and compare them to ERFs at the sources. Sensor activity as calculated using GFP is highly correlated with MEG source activity in terms of strength and latency and is posited to be a good representation of source analysis (Kasai et al., 2002, 2003).

For future research we suggest three possible options. The first is to use a source analysis algorithm that can account for as many of the generators involved in the auditory response as possible. The second is to have source analysis models that take into account the interaction of multiple sources. The third is the use of paediatric head models for source analysis. Research groups which have access to structural magnetic resonance images could use them to improve source localisation in paediatric populations. Also, research groups with access to continuous head-motion tracking technology should use this to circumvent problems surrounding variability in movement that might increase noise and compromise signal from the sensors and sources. Lastly, research groups should as much as possible use strict criteria to exclude children who move too much, and use the combined strengths of sensor and source analyses.

Tests used to measure auditory processing and language in ASD

The methods we used to measure auditory processing in the children with ASD in this research program were limited in two principal ways. First, we used a limited range of auditory stimuli. To aid the interpretation of our outcomes, our studies used highly controlled speech and semi-synthesized speech with changes and features that were perceptibly different. Previous studies using stimuli that were more speech-like have also shown a link between auditory discrimination in the brain and a social preference of speech signals, which was suggested to aid language development (Čeponienė et al., 2003; Curtin & Vouloumanos, 2013; Kuhl et al., 2005). Future research looking at the link between auditory processing and language impairment in ASD would do well to use a wider variety of stimuli, ranging from low to high frequencies as well as in its 'socialness' and more change-sizes. Examples might include the use of simple tones, complex tones, matched synthesized speech or natural speech. To specifically make auditory stimuli more ecologically valid, future mACC paradigms in studies of ASD could involve acoustic changes that are not only phonetically relevant (e.g. varying different vowels or use of

consonant-vowels), but also of varying perceptible difference, including changes much subtler than ours (e.g. 5% change, 10% change, 15% change).

Second, we did not measure the early development of children's auditory processing skills. Behavioural studies of auditory processing in adults with ASD have indicated that it is the group with a history of delayed language in childhood that also currently show enhanced or 'exceptional' pitch processing (Bonnel et al., 2010; Jones, 2009). In our studies, we did not administer retrospective parent questionnaires, which may have given us a fuller picture of auditory behaviours, functioning, and development that could not be captured by passive neural measures of auditory processing. Future studies would do well to incorporate reports of auditory hyper- or hypo-sensitivity and language delay that can be gleaned from parent questionnaires and interviews such as the Autism Diagnosis Interview-Revised (ADI-R; Le Couteur, Lord, & Rutter, 2003) and the Sensory Profile (McIntosh, Miller, Shyu, & Dunn, 1999).

Correlation does not prove causation

We acknowledge that while the findings in our studies pointed to an association between auditory processing and language impairment, this by no means is evidence for causation. Only studies that actively modify one variable (in this case, auditory processing) and observe an effect on a second variable (in this case, spoken language) can make strong conclusions about direction of causation. With this in mind, future studies of the causal role of auditory processing on language within ASD face the difficult challenge of training children with ASD for their auditory processing skills, and determining if any improvements in their auditory processing trigger (either immediately or after a period of time) improvements in their language skills.

The use of cross-sectional rather than longitudinal studies

While our studies provide a snapshot into the relationship that exists between auditory processing and language ability in ASD at one point in time, they do not provide

an insight into how the auditory processing and language skills of individuals with ASD develop with age. Brain imaging studies have found developmental changes in structure and function of auditory and language-based brain structures (Gage, Siegel, & Roberts, 2003; Keller, Kana, & Just, 2007). Thus, longitudinal studies of auditory processing and language are needed during the period where children with ASD are acquiring language to understand the rate of auditory cortex development and its relationship with language development. Future studies that set out to do this can understand the patterns of development by age-matching children in the study, and modelling the difference in growth patterns within and across different language skills (Tager-Flusberg, 2004). Further, studies in the very early stages of infancy could help establish who has typical or atypical social orienting at birth, or if mechanisms underlying a decline in auditory social perception contribute to nonverbal ASD.

The use of modest sample sizes

A great deal of time and effort was invested in the recruitment of children with ASD for the studies in this research program. Nevertheless, due to loss of participant data for various reasons in each study, we were left with modest samples of children with ASD and TD (around 15-20 participants in each group). One consequence of our modest sample sizes was that in Study 1 and Study 4 we were unable to create multiple TD groups with different ages. Fortunately, we were able to mitigate this problem using ICCs to calculate within-subjects comparison between speech and nonspeech sensor and source ERFs. Nevertheless, future studies would do well to recruit a larger group of children in order to make better comparisons to average waveforms for each age tested (e.g., at 5, 6, 7, 8, 9 years of age).

Future studies of the relationship between auditory processing and spoken language in ASD would also do well to ensure that there is a wide range of spoken language abilities in the ASD. In Study 4, we inadvertently recruited a group of children with ASD with a

narrow range of language skills, few of whom fell well below the average range. This may explain why we failed to find an association between poor auditory discrimination and poor spoken language in the ASD group at the individual level, even though such an association appeared to be present at the group level (i.e., when the mean scores of ASD and TD groups were compared).

Finally, it would be helpful if future studies included a wider variety of control groups for comparison to ASD groups. In this research program, we compared children with ASD to children with TD in studies 1, 2, and 4. We also compared our nonverbal case study with ASD to verbal children with ASD. However, to better understand the specificity of relationship between auditory processing and spoken language in ASD, it is important to examine this relationship in a sample of children with specific language impairment, and in the case of GM, children with cerebral palsy.

In conclusion, it is important for future studies to recruit larger samples of children with ASD in order to capture as much variation within ASD as possible. Somewhat paradoxically, increasing the heterogeneous nature of large samples of children with ASD will help us to identify more homogenous subgroups within ASD, which in turn should improve the reliability of outcomes between studies, and help clarify the complex nature of ASD.

Final Summary

The overall aim of this research program was to better understand the relationship between auditory processing and spoken language in children with ASD. To this end, we conducted four studies, each with important theoretical and practical applications. The findings of Study 1 and Study 2 suggest that atypical left hemisphere maturation of auditory waveforms in children with ASD is associated with poor spoken language in verbal and nonverbal children with ASD. The outcomes of Study 3 suggest that the mACC offers a more reliable and time-efficient measure of neural auditory discrimination that

may be appropriate for detecting auditory processing deficits in children and individuals from clinical populations. The results of Study 4 support this suggestion, since it revealed that children with ASD on average produced significantly poorer mACC scores than children with TD. Thus, the outcomes of this research program provide new insight into auditory processing in ASD, as well as the underlying mechanisms that might give rise to language impairment in ASD. Further, the outcomes support the use of the mACC as a neural index of auditory discrimination in children or clinical populations, the measurement of ERFs at the sensors to complement measurement of ERFs at the sources, and the examination of individual differences in the auditory processing and spoken language skills of children with ASD.

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Ethics Approvals

Ethics Approval

Ethics Secretariat <ethics.secretariat@mq.edu.au> 8 May 2014 11:03
To: Shu Yau <shu.yau@mq.edu.au>
Cc: Linda Larsen <linda.larsen@mq.edu.au>

Dear Sir/Madam,

This email is to confirm that Ms Shu Hui Yau is listed as personnel on the following HREC approved ethics application/s:

Chief Investigator: Dr Nicholas Badcock
Ref: 5201200658
Date Approved: 15/12/2012
Title: "Emotiv versus neuroscan EEG systems- a validation study "

Chief Investigator: Dr Jon Brock
Ref: HE28NOV2008-R06249
Date Approved: 16/12/2008
Title: "Cognitive and neural causes of language impairment in autism"

Chief Investigator: Dr Graciela Tesan
Ref: HE23NOV2007-R05540
Date Approved: 20/12/2007
Title: "MEG Studies of Visual and Auditory Processing"

Please do not hesitate to contact me if you have any questions.

Yours sincerely,

Dr Karolyn White
Director, Research Ethics & Integrity
Chair, Macquarie University Human Research Ethics Committee

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Office of the Deputy Vice Chancellor (Research)

Ethics Secretariat

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autism spectrum
AUSTRALIA

18 July 2012

Shu Hui Yau
Macquarie Centre for Cognitive Sciences
Macquarie University
Sydney
NSW 2109

Our Ref: 1217

Dear Shu

Auditory processing and language impairment in children with ASD

Thank you for submitting the above research proposal to the Aspect Research Approvals Committee. The committee is pleased to approve your proposal.

This approval will remain valid for one year from the date of this letter. Please advise us when your research is completed or discontinued. Aspect requests that you also provide a summary of research results upon completion.

Should you require further assistance with your recruitment or research, please contact me on the email address or telephone number below.

Yours sincerely,

Susanna Baldwin
Research Officer
Autism Spectrum Australia (Aspect)
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Seven Hills NSW 1730

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