THE NEURODEVELOPMENTAL BASIS OF HUMAN ACTION SOUND PROCESSING IN TYPICALLY DEVELOPING CHILDREN, CHILDREN WITH AUTISM SPECTRUM DISORDERS, AND TODDLERS AT RISK FOR AUTISM

By

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A thesis submitted to the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

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The University of Birmingham
November 2013

Abstract

The work presented in the current thesis explored the nature, time-course, and neurodevelopmental trajectory of the brain mechanisms underlying the perceptual processing of auditory social versus non-social stimuli in typically developing young children, toddlers and young children with autism spectrum disorders, and toddlers who are at risk of developing autism. This was completed through the use of a novel auditory-auditory repetition suppression event-related potentials (ERP) paradigm, which included sounds produced by human actions and non-human/environmental sounds. Standardised behavioural measures were also used for the matching of the groups on language ability, the behavioural characterisation of children on the autism spectrum, and the investigation of the relationship between brain activity and cognitive and social communication skills. The results revealed developmental changes in auditory social processing across two typically developing age groups, as well as atypicalities in both social and non-social processing mechanisms in children with autism spectrum disorders and toddlers at high-risk of developing autism. Together, these findings make a notable contribution to our understanding of the mechanisms underlying typical and atypical development of auditory social information processing.

To my parents,

and to the memory of my grandfather

and my best friend, Nikolaos

ACKNOWLEDGEMENTS

Firstly, I would like to express my gratitude to my PhD supervisor, Dr. Joe McCleery, who gave me the opportunity to pursue a doctoral degree in Developmental Neuroscience and implement this research in children with autism and their younger siblings. I would also like to thank him for his thorough guidance and continuous support throughout my postgraduate studies, and for giving me the opportunity to broaden my knowledge and experience on numerous occasions over the past few years of my career.

Second, I would like to thank Dr. Rita Ceponiene for her contribution to the development of the experimental design employed in the studies presented in the current thesis.

Third, I would like to thank Autistica for funding the third study presented in this thesis, as well as the British Autism Study of Infant Siblings (BASIS) Network and the Peach Network for their support and help with recruitment of families with children with ASD and high-risk toddlers. Similarly, I am grateful to all the family support groups and local schools in Birmingham and West Midlands that helped me spread the word about the present studies in children with autism and make them happen. Most importantly though, I would like to say a big thank you to all the families that took part in my studies and supported this research by spending hours or even entire weekends in the lab with our team; a special thanks to Becky and her son R., who have been a real inspiration to me and have motivated me to keep on working hard and trying my best, because…everything is possible!

Next, I would like to say a special thanks to all my friends and colleagues at the Infant and Child Lab of the University of Birmingham, who supported me in various ways and made my PhD an exciting journey, despite the difficulties I had to face. A special thanks to: Kate Graham, Dr. Katerina Kantartzis, Alena Galilee, Tash Elliott, Daniella Watson, Zahida Begum, Els Chadwick and Matt Cranwell, for their daily support and help with this research. Also, a special thank you to Georgia Stratakou, Eva Papoulia, Evi Argyriou, Maria Dagioglou, Dr. Chrysa Pornari and Kathryn Walsh for always being there for me and listening patiently.

Most importantly, I would like to thank my family, my parents, and my sister and brother for always being there for me and for their endless love and support at every stage of my life and career.

Last but not least, the biggest thank you goes to my partner, Dimitrios, for his love and invaluable moral support and patience, and for his endless effort to make me happy, even in the hardest times - this PhD would have never been completed without him.

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LIST OF ABBREVIATIONS

ADOS-G – Autism Diagnostoc Observation Schedule-Generic

ASD – Autism Spectrum Disorders

BAP – Broader Autism Phenotype

BAS – British Ability Scales

CA – Chronological Age

CDI-II – Communicative Development Inventory

EEG - Electroencephalography

ERPs – Event-Related Potentials

fMRI – functional Magnetic Resonance Imaging

fNIRS – functional Near-Infrared Spectroscopy

HR – High Risk

LR – Low Risk

MMN – Mismatch Negativity

MNS – Mirror Neuron System

MSEL – Mullen Scales of Early learning

PLDs – Point-Light Displays

Q-CHAT – Quantitative Checklist for Autism in Toddlers

RS – Repetition Suppression

SCQ – Social Communication Questionnaire

STS – Superior Temporal Sulcus

TD- Typically Developing

VA – Verbal Age

STATEMENT OF AUTHORSHIP

Chapter 3 is under submission as:

Stefanidou, C., Ceponiene, R, & McCleery, J.P. (under submission). Neural time-course of mechanisms for the processing of human action sounds in toddlers and children. *Journal of Social, Cognitive and Affective Neuroscience.*

Chapter 4 is under submission as:

Stefanidou, C., Ceponiene, R., & McCleery, J.P. (under submission). Neural time course of mechanisms for the processing of human action sounds in children with autism spectrum disorders. *Journal of Autism and Developmental Disorders.*

INTRODUCTION

Human motion provides reliable information about the recognition and understanding of actions, intentions, and affective states of other people (Blakemore & Decety, 2001; Blake & Shiffrar, 2007). Therefore, the detection and perception of sensory, motor, and affective aspects of human movement is likely to be crucial for the facilitation and development of communication and social interaction skills from infancy through adulthood. In fact, previous studies in infants have demonstrated that even neonates are able to detect biological from non-biological motion (Simion, Regolin & Bulf, 2008). In addition, a growing body of recent research has shown that cortical brain mechanisms specialized for the perception of biological motion and human actions have begun to develop by 8 months of age (e.g. Hirai & Hiraki, 2005; Reid, Belsky & Johnson, 2005; Reid, Hoehl & Striano, 2006; Southgate, Johnson, Osborne, & Csibra, 2009).

The investigation of neuroanatomical structures and brain functions underlying social perception, including biological movement and human action perception, are of great importance for deepening our understanding of both typical and atypical social development, and have been studied extensively over the past two decades (e.g., Carter & Pelphrey, 2006). For example, individuals with autism spectrum disorders (ASD) have been found to exhibit atypicalities in the activation of neural mechanisms that have been associated with the visual processing of human actions in neurotypical individuals (e.g. Bastiaansen et al., 2011; Bernier, Dawson, Webb, & Murias, 2007; Dapretto et al., 2005; Martineau, Andersson, Barthélémy, Cottier, & Destrieux, 2010; Martineau, Cochin, Magne, & Barthelemy, 2008; Oberman et al., 2005; Oberman, Ramachandran

& Pineda, 2008). These differences in brain functions may be associated with communication and social interaction difficulties experienced by individuals with ASD (American Psychiatric Association, 2013). In the current thesis, we examine whether such atypicalities are also present in the auditory modality in children with ASD and toddlers at risk for autism.

Aims and Objectives

The aim of the present studies was to investigate the perceptual processing of human versus non-human action sounds in typically developing young children, young children with autism, and toddlers at high risk of developing autism, in order to establish the neurodevelopmental trajectory of human action sound processing in these groups through the use of electrophysiological measures.

Study 1 - Specific Aim: To investigate and establish the time-course and early neurodevelopmental trajectory of human action sound processing mechanisms in typically developing two-year old toddlers and four- to five-year old children. This was completed through the use of a novel, auditory-auditory repetition suppression, event-related potentials (ERPs) assessment, recorded from a high-density (128-channel) Electroencephalography (EEG) sensor net.

Study 2 - Specific Aim: To examine whether the perceptual processing of human and non-human action sounds is atypical in four- to six-year old children with autism when compared with typically developing children. This was completed by applying the auditory-auditory repetition suppression ERP assessment used in Study 1 to this

population. The relationships between verbal and nonverbal ability, as well as communication and social skills, with brain activity were also examined in both the autism and control participant groups.

Study 3 – Specific Aim: To investigate the perceptual processing of human and non-human action sounds in two- to three-year old toddler siblings of children with autism, who are at higher risk for developing the disorder, and to examine whether the latter present with similar neural processing mechanisms as children diagnosed with autism. To this end, the auditory-auditory repetition suppression ERP assessment used in Studies 1 and 2 was also utilised in this study. Toddlers at high risk for autism were compared with low-risk toddlers with no family history of an ASD on this measure. In addition, in a second set of analyses, an additional group of toddlers with clinical/diagnostic ASD behavioural traits was also compared with both high-risk and low-risk toddlers. The relationships of verbal and nonverbal ability, as well as communication and social skills, with brain activity were also examined in all participant groups.

Structure of the Thesis

Chapter 1 presents a comprehensive review of the literature on behavioural, electrophysiological, and neuroimaging research studies of biological motion and action perception in typical and atypical development across the life span. More specifically, the first section of Chapter 1 outlines previous behavioural and neuroimaging studies of human action and biological motion processing in typically developing infants, children, and adults. The second section of the literature review describes behavioural research

studies of social attention and action perception in autism, as well as the existing body of literature in human action and biological motion processing in children and adults with ASD. Finally, the last section of Chapter 1 outlines previous research evidence on the Broader Autism Phenotype (BAP) in parents and siblings of individuals with ASD, as well as a growing body of recent behavioural and electrophysiological research on social and communication development, social attention, and social processing in infant and toddler siblings of individuals with ASD.

Chapter 2 provides a description of the experimental and electrophysiological methods employed in the current studies. More specifically, it describes the stimuli and the ERP experimental paradigm, as well as the ERP assessment procedures followed in the studies presented in the following chapters. In addition, it discusses ethical considerations related to participation in the current ERP studies and the ERP assessment procedures.

Chapter 3 presents *Study 1*, which examined the time-course and neurodevelopmental trajectory of brain mechanisms associated with human versus non-human action sound processing in typically developing toddlers and young children.

Chapter 4 presents *Study 2,* which investigated whether human and non-human action sound neural processing mechanisms are atypical in children diagnosed with autism spectrum disorders compared to typically developing children.

Chapter 5 presents *Study 3,* which examined whether human and non-human action sound processing brain mechanisms are atypical in toddler siblings of children with ASD compared to low-risk toddlers. As mentioned above, in this study high-risk toddlers were also compared with toddlers with ASD.

Chapter 6 provides a summary of the current findings and discusses methodological limitations, directions for future research, and clinical implications of the present studies.

CHAPTER 1:

LITERATURE REVIEW

1. Introduction

The perception and understanding of social stimuli, including biological motion and human actions, may play a key role in social development and the understanding of social situations involving other people's actions and emotions (see also Blakemore & Decety, 2001). A natural preference for motion produced by human actions, previously observed in young infants (Simion, Regolin, & Bulf, 2008), provides evidence for the development of social processing mechanisms from a very early age. In fact, the development of "social brain mechanisms" early on in human development has been documented by several recent studies in infants younger than 1 year of age (e.g. Hirai & Hiraki, 2005; Reid, Belsky & Johnson, 2005). These uncovered neural mechanisms have been associated with the perceptual processing of faces, human actions and non-speech human vocalizations (e.g. Lloyd-Fox, Blasi, Mercure, Elwell, & Johnson, 2012; Paulus, Hunnius, Van Elk, & Bekkering, 2012; Reid, Striano & Iacoboni, 2011) and may underlie the development of social skills in young children, including joint attention and mentalizing abilities. On the other hand, the disruption of these mechanisms may be linked to social affect or communication and social interaction difficulties experienced by children diagnosed with autism or other neurodevelopmental disorders (Americal Psychiatric Association, 2013).

The following literature review outlines and discusses previous studies employing behavioural, electrophysiological or neuroimaging research methods, in order to explore the nature and development of these social processing mechanisms both in typical development, from infancy to adulthood, and the atypical social development observed in children and adults with Autism Spectrum Disorder (ASD) and high-risk infant and toddler siblings of individuals with ASD.

1.1 Biological motion and human action perception in typical development

1.1.2 Behavioural studies in biological motion perception

1.1.2.1 Biological motion perception in children and adults

In order to investigate adults' perception of human motion, several studies have used Point-Light Displays (PLDs), which were initially developed by Gunnar Johansson (1973). These are animation figures with small illuminated dots placed on their head and joints, depicting Biological Motion (BM) (Johansson, 1973). Adult observers have been found to be able to discriminate familiar from unfamiliar individuals (Cutting & Kozlowski, 1977; Loula, Prasad, Harber, & Shiffrar, 2005) and male from female figures in the PLDs from their movements (Kozlowski & Cutting, 1977; Mather & Murdoch, 1994; Troje, 2002). In addition, child observers, aged 7-10 years, have been found to be able to distinguish human from object movement in PLDs (Moore, Hobson & Anderson, 1995), although PLD orientation can affect the perception and recognition of point-light animations in both young children and adults (Mitkin & Pavlova, 1990; Pavlova & Sokolov, 2000). Other studies have shown that adults are able to identify the actions of a moving figure in a PLD (Dittrich, 1993; Norman, Payton, Long, & Hawkes, 2004) or the facial expression portrayed in a point-light animation (Bassili, 1978), as well as to perceive emotions from biological motion in dynamic PLDs (Clarke, Bradshaw, Field, Hampson, & Rose, 2005; Dittrich, Troscianko, Lea, & Morgan, 1996).

1.1.2.2 Biological motion and human action perception in infancy

The perception and detection of biological motion stimuli has been suggested to be an early capacity in human life (see Bertenthal, 1993, for a review). This notion has been supported by previous findings showing that even newborn infants prefer to attend

to visual or auditory stimuli related to human movement, such as PLDs (depicting moving human figures), human/rhesus monkey vocalizations, or speech sounds, over other forms of visual or auditory motion, such as randomly moving drifting dots (Simion, Regolin & Bulf, 2008), synthetic sounds (Vouloumanos, Hauser, Werker, & Martin, 2010), or non-speech analogues (Vouloumanos & Werker, 2007). Even neonates have been found to show a preference for upright over inverted PLDs, as they were found to look longer at upright than inverted displays (Simion, Regolin, & Bulf, 2008). This preference, driven by visual display orientation, has also been found in 4- to 6-month-old infants (Fox & McDaniel, 1982) and 2-year-old toddlers (Klin, Lin, Gorrindo, Ramsay, & Jones, 2009). In addition, other studies have revealed that 3-month-old infants were able to discriminate canonical biological motion from scrambled motion in both upright and inverted PLDs, by looking longer at scrambled motion displays (Bertenthal, Proffitt & Kramer, 1987; Bertenthal, Proffitt, Kramer, & Spetner 1987). However, slightly older infants were able to exhibit such discrimination only when the displays were upright (Bertenthal et al., 1987; Bertenthal, Proffitt & Kramer, 1987)**.** This difference in the way 3- and 5-month-old infants were found to perceive upright versus inverted biological motion displays has been suggested to be associated with increasing experience with upright human form through development (Bertenthal et al., 1987). On the other hand, in a more recent study by Slaughter et al. (2002) using static stimuli, infants younger than 18 months of age did not show any preferential attention to scrambled human figures over the normal ones. This finding suggests that motion properties of point-light animations used in previous studies may make the stimuli less ambiguous for infants to detect (Reid, Belsky & Johnson, 2005). This hypothesis was supported by the findings of Reid, Belsky, and Johnson (2005),

which revealed that 8-month-old infants were able to perceive biologically possible human movements by looking longer at video clips of impossible body movements (e.g. arm and hand moving toward an object via an impossible axis) than possible body movements (e.g. arm reaching for an object). This early capacity to detect and distinguish human motion stimuli observed in infants may be important in the development of communication and social interaction skills through infancy and early childhood.

1.1.3 Neuroimaging studies in biological motion and human action perception

1.1.3.1 Neural perceptual processing of biological motion and human movement in infancy

Previous behavioural research findings on biological motion perception in infants has given rise to the investigation of the development of neural mechanisms underlying the detection and perceptual processing of biological motion stimuli and body actions (Grossman & Johnson, 2007). In an event-related potentials (ERP) study, Reid, Hoehl, and Striano (2006) investigated how 8-month-old infants processed PLDs depicting a human figure either kicking or walking, when these displays were presented in an upright or inverted position. The authors identified a positive-going ERP component within the latency range 200-300ms over right parietal sites, which was larger in response to upright than to inverted PLDs (Reid, Hoehl & Striano, 2006). These findings were consistent with a recent near-infrared spectroscopy (NIRS) study in 7- to 8-month old infants (Ichikawa, Kanazawa, Yamaguchi, & Kakigi, 2010). More specifically, Ichikawa and colleagues (2010) reported an increased concentration of

oxyhemoglobin (oxy-Hb) in the right cortex, elicited by upright PLDs depicting facial movement when compared with static figures or inverted PLDs.

In another ERP study, 8-month old infants were found to process canonical biological motion and scrambled motion differently from each other (Hirai & Hiraki, 2005). Hirai and Hiraki (2005) reported that PLDs depicting a walking person with canonical motion, compared with PLDs with scrambled motion, elicited a larger negative-going amplitude within the latency range 200-300ms over right posterior scalp sites in infants' ERPs. They also found a smaller positive-going amplitude elicited by scrambled PL walkers over temporoparietal sites (Hirai & Hiraki, 2005). This is consistent with more recent findings by Reid, Hoehl, Landt, and Striano (2008), who examined how 8-month-old infants process canonical PLDs of kicking and walking when compared with both PLDs moving in a biomechanically impossible way and PLDs with coherent biological motion but with non-human altered body schema. The authors found that biomechanically impossible motion elicited greater positive-going, but bilateral, activity within the latency range 300-700ms over mid-parietal channels (Reid et al., 2008). Similarly, another ERP study by Marshall and Shipley (2009) demonstrated a greater, but slow, positivity within the latency range of 500-600 ms, elicited by PLDs with scrambled motion in 5-month-old infants. In contrast to Reid et al.'s (2008) findings, this positive activity was larger over the lateral parietal and temporal sites (Marshall & Shipley, 2009). In addition, Marshall and Shipley (2009) reported greater positive activity elicited by the canonical PLDs over the mid-parietal and occipital sites. Taken together, these findings may reflect developmental changes in the neural processing of visual biological motion stimuli during the first year of life.

The aforementioned findings were extended by electroencephalography (EEG) studies measuring power change in infants while watching videos of human actions. Specifically, in an EEG study of 8-month-old infants, Reid, Belsky, and Johnson (2005), identified a positive burst of gamma activity in the right fronto-temporal sites, elicited by video clips of possible human movement when compared with clips of impossible movement, only in a subgroup of infants with relatively high fine motor abilities. The authors suggested that the ability to perceive differences between possible and impossible human movement, and to recognize postural instability, may develop from the first months of life and may be related to increases in gamma activity in fronto-central sites, as previously shown by adult research (Reid, Belsky & Johnson, 2005; Slobounov, Tutwiler, Slobounova, Rearick, & Ray, 2000). They also proposed that more advanced infants may be able to perform better at both biological motion perception and production tasks, and that there may be an association between the perception of human movement and the ability to perform fine motor actions (Reid, Belsky, & Johnson, 2005).

This notion was also supported by EEG studies examining whether or not the "mirror neuron system" (MNS), previously found in adults (Rizzolatti, Fogassi & Gallese, 2001), exists in infants as well (see Marshall & Metzoff, 2011, for a review). The MNS, initially observed in macaque monkeys, has been proposed to be responsible for the "translation" of the visual representation of observed body actions into their actual motor representations in the observer (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Rizzolatti, Fogassi, & Gallese, 2001). Mirror neuron activity in the frontoparietal network is thought to be reflected in electroencephalography (EEG) oscillations in the 8-13 Hz mu frequency band recorded from electrodes over the motor

cortex (Pineda, 2005). The mu rhythm is a resting state EEG rhythm, which has been found to be 'suppressed' in humans, when mirror neurons fire asynchronously during both the execution and observation of human actions (e.g. moving hand), as opposed to non-human actions (e.g. moving object; Pineda, 2005). Previous EEG studies have reported mu suppression during simple action observation (e.g. grasping an object) even in 8- and 9-month old infants (Nystrom, Ljunghammar, Rosander, & von Hofsten, 2011; Southgate et al., 2009), but not in 6-month infants (Nystrom, 2008). Interestingly, in another EEG study, van Elk and colleagues (van Elk, van Schie, Hunnius, Vesper, & Bekkering, 2008) found stronger mu- and beta-band desynchronizations over the frontal and central midline electrode sites in 14- to 16-month old infants, while watching videos of a person crawling compared to videos of a person walking. The authors reported that the infants' neural responses correlated with their crawling experience, and suggested that human action perception in infants may be related to personal experience of the same action (van Elk et al., 2008). These findings were also supported by another study by Reid, Striano, and Iacoboni (2011) who found mu suppression in 14-month old infants only when they observed actions that they were familiar with, during dyadic interactions.

In order to investigate the potential neural overlap between action perception and action execution in infants, Marshall, Young, and Meltzoff (2011) examined 14-month-old infants' neural responses to both action observation and action execution and found EEG desynchronization in the "infant alpha" frequency range (6-9 Hz) during both conditions. However, action observation was associated with broader desynchronization over frontal, central, and parietal sites, while action execution was only associated with desynchronization in the central region (Marshall, Young & Meltzoff, 2011). These

findings were also replicated by Warreyn et al. (2013) in 18- to 30-month old toddlers, who observed central mu suppression even when the toddlers observed intransitive hand movements. Taken together, the aforementioned EEG studies in infants have provided evidence for the existence of shared functional properties between the infant central rhythm at 6-9 Hz and the adult mu rhythm in the alpha frequency range (8-13 Hz; Marshall, Young, & Metzoff, 2011), which has been found to be desynchronized during both action observation and execution in adults (Muthukumaraswami & Johnson, 2004; Pineda, Allison, & Vankov, 2000; Pfurtscheller, 2003).

Although EEG measures employed in the aforementioned studies in infants provide good temporal resolution, recent studies of social processing in infants have used functional near-infrared spectroscopy (fNIRS), which is similar to functional Magnetic Resonance Imaging (fMRI) and can provide better spatial resolution than EEG. More specifically, an fNIRS study by Lloyd-Fox et al. (2009) examined how 5-month old infants process social dynamic stimuli (an actor playing "peek-a-boo") relative to non-social static (helicopter) or dynamic (moving mechanical toys) visual stimuli. Their findings revealed greater haemodynamic responses in the temporal region to social stimuli, when compared with non-social static or dynamic stimuli (Lloyd-Fox et al., 2009). These results suggested that greater neural activation in response to social cues were not driven by the motion properties of the social stimuli and were replicated in a more recent fNIRS study in 5-month old infants by the same research group (Lloyd-Fox, Blasi, Everdell, Elwell, & Johnson, 2011). Interestingly, the difference in the latter was that three different types of biological motion were presented to the infants, including eye, mouth, and hand movements, performed by the same actress (Lloyd-Fox et al., 2011). Eye movements elicited greater activation in the frontal-

temporal region, mouth movements were associated with greater right temporal activity, and hand movements elicited greater neural responses in the frontal cortex. Notably, however, there was a greater tendency for right hemisphere activation in response to biological motion overall (Lloyd-Fox et al., 2011).

1.1.3.2 Neural perceptual processing of biological motion in children

As most previous neuroscientific research has focused on the development of perceptual processing of human movement over the first year of life and on perceptual processing of biological motion in adults, there is very little research evidence regarding the development of neural mechanisms underlying the perception of human actions and biological motion in young children. A recent EEG study by Lepage and Theoret (2006) is one of the very few studies investigating the neural mechanisms underlying human action processing in pre-school and school-aged children. The authors examined mirror neuron system functioning in 4- to 11-year old children, and found mu rhythm suppression in response to both action observation and execution (Lepage & Theoret, 2006). Interestingly, mu suppression was observed to be stronger in response to visual stimuli of hand movements (e.g. grasping) when compared with stimuli of intransitive movements (e.g. flat hand movement; Lepage & Theoret, 2006).

In another study using fMRI, Carter and Pelphrey (2006) investigated how 7- to 10-year old children processed animated figures depicting biological (human, robot) versus non-biological motion (mechanical motion, grandfather clock). Their findings provided evidence for a network of social brain regions, associated with biological motion over non-biological motion perception in childhood (Carter & Pelphrey, 2006). This neuroanatomical network included the bilateral Superior Temporal Sulcus (STS)

bilaterally, the lateral fusiform gyrus (FFG) bilaterally, the frontal gyri (FG), the parietal-temporal-occipital fossa (PTOF), the intraparietal sulcus (IPS) bilaterally, and the superior and inferior parietal lobules bilaterally (Carter & Pelphrey, 2006). Frontal, parietal, and temporal regions were also found to be preferentially engaged for the perception of biological motion when compared with scrambled motion in PLD walkers by adolescents and young adults (Freitag et al., 2008). More specifically, Freitag et al. (2008) identified a bilateral temporo-parietal network, comprising the STS, and suggested that it may be associated with the perception of unintentional biological motion (Freitag et al., 2008).

Apart from visual stimuli associated with body movements, another type of biological motion that has also been studied in children is facial movements, including eye-gaze shifts. For example, Mosconi and colleagues (2005) (Mosconi, Mack, McCarthy, and Pelphrey, 2005) investigated neural processing of eye-gaze direction in 7- to 10-year old typically developing children. According to the authors, as a type of dynamic facial cue providing social information about other people's actions and intentions, eye-gaze shifts and movements are biological motion cues that could be highly informative for social perception (Mosconi et al., 2005). In their fMRI study, Mosconi et al. (2005) used an animated character making eye-movements which were either congruent or incongruent with the location where an object appeared on the screen. Their findings revealed a frontal, parietal, and temporal network associated with eye-movement processing, which was previously found in adults as well (Mosconi et al., 2005; see also Pelphrey et al., 2003).

1.1.3.3 Neural perceptual processing of biological motion and human action in adults

The aforementioned developmental research findings are consistent with other findings from previous neuroimaging research of biological motion processing in adults. Previous fMRI studies have indicated that neural processing of visual biological motion displays and human movement videos, including facial movement, eye-gaze, hand actions, and body movements, has been associated with cortical activity in the occipitotemporal cortex, including the STS (especially over the right posterior sites), the fusiform gyri, fronto-central regions, and the parietal cortex (Beauchamp, Lee, Haxby, & Martin, 2002; Beauchamp, Lee, Haxby, & Martin, 2003; Buccino et al., 2001; Calvert et al., 1997; Grossman et al. 2000; Iacoboni et al., 1999; Pelphrey et al., 2003; Puce, Allison, Bentin, Gore, & McCarthy, 1998; Safford, Hussey, Parasuraman, & Thompson, 2010; Saygin, Wilson, Hagler, Bates, & Sereno, 2004; Vaina, Solomon, Chowdhury, Sinha, & Belliveau, 2001; Wheaton, Thompson, Syngeniotis, Abbott, & Puce, 2004). However, the activation of the ventral temporal cortex, and especially the STS, was found to be weaker in response to PLDs than to videos of human movement by Beauchamp et al. (2003), suggesting that information provided only by the latter, such as form, texture, or colour of the stimuli, is strongly associated with activity in the STS. On the other hand, object / non-biological motion processing has been particularly associated with greater activation in the inferior temporal sulcus (ITS) and the middle temporal gyrus (MTG; Beauchamp et al., 2002; Beauchamp et al., 2003; Safford et al., 2010).

Other studies using ERPs have identified a visual biological motion processing neural network over temporo-parietal sites (Wheaton, Pipingas, Silberstein, & Puce, 2001), and more specifically over the right posterior cortex. This network also included

right occipito-temporal sites (Hirai, Fukushima & Haraki, 2003; Hirai & Hiraki, 2005) and right temporal and superior temporal gyrus (Jokisch, Daum, Suchan, & Troje, 2005). Furthermore, other EEG and fMRI studies that have provided evidence for the "mirror system hypothesis" in humans (Rizzolatti, 2005) have shown that the observation and execution of movements share a common cortical network, comprising the motor and frontal cortices (Cochin, Barthelemy, Roux, & Martineau, 1999; Iacoboni et al., 1999; see also Rizzolatti, Fogassi & Gallese, 2001).

1.1.3.4 Neural perceptual processing of action-related sounds in adults

The perception of human motion and actions has been found to be modulated not only by visual, but also auditory cues and inputs (Aglioti & Pazzaglia, 2010). Previous single-cell recording research has revealed the existence of both auditory and auditory-visual mirror neurons in monkeys, which have been found to discharge when monkeys perform an action as well as when they hear an action-related sound (Kohler et al., 2002). These findings, in turn, have led several research groups to the investigation of body action sound processing in humans.

Recent fMRI studies have attempted to identify a neural network associated with both visual and auditory human action processing and the actual execution of an action (e.g. Gazzola, Aziz-Zadeh & Keysers, 2006). For example, in an fMRI study by Kaplan and Iacoboni (2007) a common fronto-parietal network was found to be modulated by both visual and auditory inputs related to a paper-ripping action. In addition, more recent fMRI findings by Ricciardi et al. (2009) revealed that both passive listening to action-related sounds and performing motor pantomimes activated a common, left-lateralised premotor and temporal-parietal neural network in both congenitally blind and

sighted participants. Interestingly, the authors reported that the MNS activity was larger in response to familiar than unfamiliar action sounds in both groups of participants (Ricciardi et al., 2009). Moreover, another fMRI study by Bidet-Caulet, Voisin, Bertrand, and Fonlupt (2005) identified an auditory attentional network of bilateral frontal and parietal areas, as well as the posterior STS, which were activated in response to the sound of walking footsteps in adult participants.

Previous EEG/ERP studies have also provided evidence for the latency of human-action sound processing by utilising both "mismatch negativity" (MMN) and "repetition suppression" (RS) experimental paradigms. The "mismatch negativity" (MMN) or "passive oddball" paradigm is a standard methodological technique, based on a memory-based process, that has been used in numerous EEG/ERP studies examining neural responses to rare deviant stimuli appearing randomly in a stream of standard stimuli (e.g., Hauk, Shtyrov, & Pulvermuller, 2006; see also May & Tiitinen, 2010, for a review). Hauk, Shtyrov and Pulvermuller (2006) used an MMN paradigm in order to compare adults' ERP responses to action-related auditory stimuli (finger and tongue clicks) with their responses to non-action-related sounds, but with similar physical features. Their findings revealed larger MMNs produced by natural action-related sounds than control stimuli at 100 ms, with the hand action-related sounds producing greater activation over the left fronto-central region. Similar latency effects were observed in another ERP study that utilised a visuo-auditory MMN paradigm and found a larger N100 in response to a hand action-related sound (banging sound) preceded by a deviant picture (hammer hitting a finger of the hand fixing the nail), when compared with ERP responses to a hand-action related sound (banging sound) preceded by a

standard picture (hammer hitting a nail) (Ullsperger, Erdmann, Freude, & Dehoff, 2006).

In an auditory evoked potentials (AEP) study, Murray and colleagues (2006) (Camen, Andino, Bovet, & Clarke, 2006) used an "oddball" target detection task, which included sounds of living objects (e.g. animal sounds, baby crying, sneezing) and sounds of man-made objects (e.g. musical instruments, car horn, telephone). The authors found larger early neural responses to man-made relative to living sounds over the right temporal and left frontal regions but prolonged activity in response to living sounds over premotor and temporal regions at a later stage of processing (Murray et al., 2006). These findings provide additional evidence for the existence of distinctive neural mechanisms associated with the perceptual processing of sounds produced by objects relative to actions or voices produced by human beings or other living objects, such as animals (Murray et al., 2006). However, high-level auditory processing of man-made object or tool-related sounds has been highlighted in other fMRI studies, which have revealed the activation of a left-lateralised mirror network in response to tool-related sounds (e.g. Lewis, Brefczynski, Phinney, Janik, & DeYoe, 2005; see also, Lewis, 2006), as opposed to non-tool mechanical or environmental sounds. In contrast, the latter have been found to activate the anterior superior temporal gyri, and the parietal and occipital regions respectively (Engel, Frum, Puce, Walker, & Lewis, 2009). Lewis et al. (2005) argued that the involvement of a previously identified human action processing network in the perceptual processing of tool-related sounds may reflect the "activation" of a reasoning mechanism associating these sounds with motor actions that are likely to produce them (see also, Rauschecker, 2011).

Other EEG/ERP or fMRI studies have used "repetition suppression" (RS), which is a methodological technique involving the presentation of a stimulus followed by either the direct repetition of a same stimulus from the same perceptual category or its replacement by a stimulus from a different perceptual category (non-repetition) (Baldeweg, 2006; Grill-Spector, Henson & Martin, 2006). When the stimulus class is repeated, the brain mechanisms are suppressed and the neural activity is reduced, as a result of neural adaptation to the perceptual properties of the stimulus; in contrast, when a stimulus is followed by a different stimulus type, the brain mechanisms are "released," as a result of the increase in prediction error (Baldeweg, 2006; Grill-Spector, Henson, & Martin, 2006; Todorovic & de Lange, 2012). Several studies have utilised RS experimental paradigms in order to examine RS effects to social stimuli, such as faces (e.g. Ishai, Pessoa, Bikle, & Ungerleider, 2004; Kuehl, Brandt, Hahn, Dettling, & Neuhaus, 2013; Schweinberger, Huddy, & Burton, 2004; Vizioli, Rousselet, & Caldara, 2010), body parts (e.g. Kovacs et al., 2006), speech (e.g. Kim, Lee, Shin, Kwon, & Kim, 2006; Olichney et al., 2000; Swick, 1998), as well as action-related sounds (e.g. Giusti, Bozzacchi, Pizzamiglio, & Di Russo, 2010; Pizzamiglio et al., 2005).

Pizzamiglio et al. (2005) developed a visuo-auditory RS ERP paradigm, in order to investigate the neural processing of action-related sounds in adults. Their ERP paradigm included the presentation of action- and non-action-related visual words followed by auditory stimuli from the same or a different perceptual category (either mouth/hand action- or non-action-related sounds). Their findings revealed that incongruent action sound trials, in which the action-related sound was preceded by a non-action-related visual word, elicited greater activity over the frontal and temporal channels (peak at 280ms), whereas the incongruent non-action sound trials were

associated with greater activity over the temporal sites (peak at 320ms). In addition, action-related sound processing was found to be left lateralised, as opposed to non-action-related sound processing, which was bilateral. These findings provide additional evidence for the existence of distinctive neural mechanisms underlying the perceptual processing of action- relative to non-action-related sounds. Interestingly, the latency of those components appears to be similar to the latency repetition effects (200-500ms) previously found to words over the frontocentral and temporoparietal channels (Kim et al., 2006). In addition, differences in the latencies of neural responses to the action-related sound stimuli found by Pizzamiglio et al. (2005) when compared with findings by MMN EEG/ERP studies (Hauk, Shtyrov, & Pulvermuller, 2006; Ullsperger et al., 2006) may reflect differences in the experimental design and / or the complexity of the stimuli used (Hauk, Shtyrov & Pulvermuller, 2006).

Following up the Pizzamiglio et al. (2005) study, in an event-related fMRI study, Galati et al. (2008) used a similar visuo-auditory RS experimental paradigm and reported that action-related sounds activated the left inferior frontal and posterior temporal regions bilaterally. On the other hand, non-action related sounds elicited greater activation in the right middle frontal and parietal areas, as well as in the superior temporal region bilaterally (Galati et al., 2008). Pizzamiglio et al. (2005) findings were also replicated by Giusti and colleagues (2010), who employed a visual and an auditory, RS ERP paradigm, in order to explore further the neural mechanisms that are associated with visual and auditory human action processing separately. The difference between the Giusti et al. (2010) and the Pizzamiglio et al. (2005) experimental paradigms was that the former included stimuli from the same modality in each paradigm (e.g. auditory hand action followed by another auditory hand action or non-action-related sound, or

silent clip of hand action followed by another silent clip of a hand action or object). In addition, in accordance with Pizzamiglio et al. (2005) findings, Giusti and colleagues (2010) also found a lateralization effect for action-related sound processing, as well as a different time course for neural processing of action-related relative to non-action-related sounds over frontal, temporal, and parietal electrode sites. Their findings provided additional evidence for the existence of distinctive neural mechanisms underlying the perceptual processing of both visual and auditory action-related and non-action-related stimuli (Giusti et al., 2010).

1.1.3.5 Neural perceptual processing of action-related sounds and speech in infancy

Although previous adult research has provided evidence for the existence of distinctive neural mechanisms underlying the perceptual processing of human and non-human action-related sounds (e.g. Giusti et al., 2010; Hauk, Shtyrov, & Pulvermuller, 2006; Pizzamiglio et al., 2005), little is currently known about the existence of such auditory processing neural mechanisms in infants and children. In a recent EEG study in 8-month-old infants, Paulus and colleagues (2012), reported stronger EEG mu rhythm (6 to 9 Hz) desynchronization over frontal electrode sites elicited by sounds that were previously the effect of the infants' own actions, when compared with unfamiliar or non-action related sounds. However, no hemispheric lateralisation was found for action-related sound processing (Paulus et al., 2012), as previously reported in adult research (Hauk et al., 2006; Pizzamiglio et al., 2005). These findings provide preliminary evidence for the development of human action sound processing mechanisms in infancy (Paulus et al., 2012).

Of course, action-related sounds are not limited to body action sounds or sounds produced by human actions on objects, but vocal and speech sounds, as well. In a recent fNIRS study in 4- to 6-month old infants, Lloyd-Fox et al. (2013) found greater haemodynamic responses to vocal stimuli (e.g. sneezing, coughing, laughing) over the right cortex, in the STS region, when compared with non-vocal stimuli, such as toy sounds, which elicited greater activity over the left posterior cortex. Their results replicated previous findings of a progressive specialisation of specific brain areas, and especially the STS, for human voice processing in 4- to 7-month old infants (Grossman, Oberecker, Koch, & Friederici, 2010; Lloyd-Fox et al., 2012). Moreover, other fMRI and ERP studies have shown that young infants can be sensitive to familiar versus unfamiliar human voices, as well as to emotional prosodies in human voices by presenting with differential electrophysiological responses (e.g. Dehaene-Lambertz et al., 2010; Grossman, Striano and Friederici, 2005; Purhonen, Kilpeläinen-Lees, Valkonen-Korhonen, Karhu, & Lehtonen, 2004). For example, as in the Paulus et al. (2012) study, Purhonen et al. (2004) reported differences in 4-month old infants' electrophysiological responses to familiar and unfamiliar auditory stimuli over frontal and central regions. These included their mothers' voice saying the word "hi" in finnish, when compared with an unfamiliar voice saying the same word. More specifically, the authors reported more negative ERP responses to the familiar voices after 350ms, and they argued that this difference might have been driven by the infants' increased attention to their mothers' voice (Purhonen et al., 2004). Similarly, Grossman, Striano, and Friederici (2005) found a more negative ERP amplitude in the 300-600ms latency range over temporal channels in response to angry voices compared to neutral or happy

voices in 7-month old infants, and explained this effect as a result of possibly increased attention to angry prosodies.

Interestingly, distinctive neural mechanisms associated with processing of speech relative to non-speech sounds, such as music, were also replicated in a more recent fMRI study involving 2-month old infants (Dehaene-Lambertz et al., 2010). In addition, an fMRI study in 3-month old infants by Dehaene-Lambertz, Dehaene, and Hertz-Pannier (2002) demonstrated that speech processing was already left lateralised at this early age. Their findings also revealed the activation of right prefrontal cortex only in awake infants, which, according to the authors, may be associated with the activation of memory mechanisms of prosodic contours (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002). In older infants, Mills and colleagues (2004) found that ERPs to known/familiar words differed from phonetically different nonsense/unfamiliar words in both 14- and 20-month old infants. These findings are similar to other findings from human action processing studies in infants revealing differences in brain activity elicited by familiar relative to unfamiliar actions (e.g. Reid, Belsky, & Johnson, 2005; van Elk et al., 2008; Reid et al., 2011).

Other studies attempting to investigate the neural mechanisms and processing steps underlying speech and gesture perception have used match/mismatch ERP paradigms (e.g. Dehaene-Lambertz & Baillet, 1998; Dehaene-Lambertz & Dehaene, 1994; Sheehan, Namy & Mills, 2007). For example, Dehaene-Lambertz and Dehaene (1994) used an MMN ERP paradigm and found syllable (/ba/ versus /ga/) repetition effects at a late stage of processing (400ms) over the frontal region in three-month-old infants. This effect was later shown to be associated with the phonological perception

rather than the acoustical discrimination of syllables within approximately the same latency range (Dehaene-Lambertz & Baillet, 1998).

In addition, Sheehan, Namy, and Mills (2007) used an ERP paradigm in order to investigate the mismatch effect of words and gestures in 18- and 26-month old toddlers. More specifically, in their match/congruent trials, videos of a person speaking a word or performing a symbolic gesture were followed by a picture of the object previously named or a picture represented by the preceding symbolic gesture, respectively (Sheehan, Namy & Mills, 2007). On the other hand, in the mismatch/incongruent trials, the videos of a person speaking a word or performing a symbolic gesture were followed by a picture of an object that did not match the preceding word or symbolic gesture (Sheehan, Namy, & Mills, 2007). Sheehan and colleagues (2007) found an N400 congruency effect for both words and gestures over the frontal, temporal and parietal sites in 18-month old infants, which, however, did not hold for gestures and was observed only over the temporal and parietal channels in 26-month olds. These findings provide additional evidence for the existence of possible shared neural mechanisms underlying language and gesture processing (see also, Bates & Dick, 2002), as well as for a developmental shift in relation to semantic processing of gestures in early childhood (Sheehan, Namy, & Mills, 2007). This developmental shift may be associated with a U-shaped developmental function previously described in young children, according to which symbolic gesture comprehension decreases from 18 to 26 months and then increases again by four years of age (Namy, Campbell, & Tomasello, 2004; Sheehan, Namy, & Mills, 2007; see also Shore, Bates, Bretherton, Beeghly, & O'Connell, 1990). According to Namy and colleagues (2004), children may become more conservative in their communicative conventions at two years of age, as they need

to be able to associate new gestures with their previous knowledge of an action in order to learn them.

Given the evidence provided from previous behavioural and neuroimaging studies on the perceptual processing of biological motion and human actions in infants, children and adults, as well as on the perceptual processing of action-related sounds in adults and infants, it would be interesting to investigate the neural mechanisms underlying action-related sound processing in young children, as well. The current research addresses questions relating to the neurodevelopmental trajectory of action-related sound processing mechanisms across different age groups in early childhood, as well as the relation between auditory gesture processing and language development. The investigation of human action sound processing mechanisms in young children may, in fact, enrich our knowledge of gesture and language development, which have been suggested to be mediated by shared brain mechanisms (Bates & Dick, 2002; Gentilucci & Volta, 2008). Notably, the human action processing network of the brain has also been suggested to be associated with the understanding of social intentions from motion and the prediction of future actions of other human agents (Blakemore & Decety, 2001). Therefore, the investigation of auditory gesture neural processing mechanisms in typical development may also contribute to the development of research methodologies and techniques for the investigation of similar neural mechanisms in clinical groups with communication and social interaction deficits, such as individuals with Autism Spectrum Disorders (ASD; American Psychiatric Association, 2013).

1.2 Social processing in Autism Spectrum Disorders

1.2.1 Introduction

Autism is one of the most severe neurodevelopmental disorders with a considerable increase in prevalence over the past few years (currently 60 children in 10,000), a devastating impact on families, and a very high cost to society (DiCicco-Bloom et al., 2006; Fombonne, 2004; Knapp, Romeo & Beecham, 2009; Levy, Mandell & Schultz, 2009). It appears that the first description of autism-like behavioural traits was by Harlan Lane in his book "The Wild Boy of Aveyron" in the 19th century (Wing, 1996). He described a boy whose behavioural patterns would be similar to the behavioural profile of a child diagnosed with autism today (Wing, 1996). However, the first individual who officially described autism was Leo Kanner, in 1943. In his paper, Kanner (1943) described eleven children who presented with a similar clinical picture, including speech abnormalities, lack of social or emotional contact with other people, intense interest in manipulating objects, repetitive behaviours, and relatively higher levels of non-verbal skills (see also Wing, 1996). Kanner (1943) referred to these behavioural patterns as "autistic disturbances of affective contact," and he suggested that early infantile autism is a condition in which children lack motivation and interest in communication and social interaction with other people from birth (see also, Volkmar & Klin, 2005). At the same time, Hans Asperger (1944) described a higher-functioning type of autism, Asperger's Syndrome, including good vocabulary but monotonous or repetitive speech, inappropriate social behaviour, and intense or restricted interests in particular subjects (Wing, 1996).

The current clinical description of autism is similar to those provided by Kanner (1943) and Asperger (1944), and includes qualitative impairments in communication

and social interaction skills, as well as restricted interests and repetitive behaviours (American Psychiatric Association, 2000). Autism is currently thought to be a continuum or a "spectrum" disorder and has been described as a condition that is not always easily distinguished from typical development, especially in high-functioning individuals (Wing & Gould, 1979; Wing, Gould, & Gillberg, 2011; see also McCleery, Stefanidou, & Graham, 2011, see *Appendix C1*). According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), Autism Spectrum Disorders (ASDs), termed as Pervasive Developmental Disorders, included four different subtypes: Autistic Disorder, Asperger's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) (American Psychiatric association, 2000). However, this was changed in the recently published Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), which describes autism as a single Autism Spectrum Disorder, including all potential subtypes of autism under a single diagnostic umbrella (American Psychiatric Association, 2013; see also Szatmari, 2011; Wing, Gould, & Gillberg, 2011). Although this major change in autism diagnostic categories has several implications for the autism clinical and research community, the new single diagnostic category still includes the "triad of impairments" in autism, initially discussed by Wing & Gould (1979; see also, Wing, Gould, & Gillberg, 2011). Communication and social interaction deficits (described as one conjoined problem in the DSM-V), and restricted behaviour are still the behavioural criteria for a diagnosis of an Autism Spectrum Disorder (American Psychiatric Association, 2013).

1.2.2 Theoretical models in Autism Spectrum Disorders (ASD)

Numerous genetic, behavioural, and neuroimaging studies conducted over the past few decades have attempted to provide answers about the causality of autism, and to contribute to early screening and intervention, as well as to a better understanding of early development, psychological functioning, and the neural underpinnings of social and communication deficits in ASDs (e.g. Baron-Cohen, 1995; Boyd et al., 2010; Dawson, 2008; Fountain, Winter, & Bearman, 2012; Hallmayer et al., 2011; Happe & Frith, 2006; Hughes, 2007; Kennedy & Courchesne, 2008; Mizuno, Villalobos, Davies, Dahl, & Müller, 2006; Russell, 1997; Schultz, 2005; Toth, Munson, Meltzoff, & Dawson, 2006). During the 1960s and '70s, it started becoming clear in the scientific community that autism was a developmental disorder rather than an emotional disorder caused by parents' behaviour, as previously suggested by psychoanalysts (e.g. Mahler, 1952; see also Lord & Bailey, 2005; Wing, 1996). The first twin study of autism by Folstein and Rutter (1977) provided evidence for the notable genetic liability of the disorder, which was then followed by numerous genetic and twin studies, revealing that a complex combination of genetic and environmental factors is involved in the emergence of autism (e.g. Gupta, 2007; Hallmayer et al., 2011; Happe & Ronald, 2008; see also McCleery, Stefanidou, & Graham, 2011).

At the same time, other studies investigated the cognitive processing style of autism and established some key psychological theories and models, including the executive dysfunction theory, the weak central coherence theory, and the Theory of Mind (e.g. Baron-Cohen, 1995; Happe & Frith, 2006; Russell, 1997). Executive function is an umbrella term covering several higher cognitive capacities, such as planning and monitoring behaviour, inhibition, set-shifting, and holding information in

working memory, and has been suggested to be impaired in individuals with an ASD (e.g. Russell, 1997). On the other hand, "Weak central coherence" refers to the detail - focused processing style that has been found to characterise a lot of individuals on the autism spectrum. In fact, this detail - focused processing style can be regarded as an index of superior performance in local processing rather than impairment in global processing, as previously suggested by Happe and Frith (2006). Finally, the Theory of Mind refers to the ability to understand other people's actions and represent their intentions, mental states and beliefs, which has also been found to be delayed in individuals with an ASD (Baron-Cohen, 1995; Baron-Cohen, Leslie, & Frith, 1985). However, this theory was recently revised by Baron-Cohen (2009), who suggested a new psychological model, combining impaired or delayed empathy with intact or higher skills in systemizing. The latter refers to the analysis or construction of any type of systems, within any type of context. This model emphasizes the imbalance between impaired or delayed social versus enhanced non-social processing in autism, which has been previously documented by both behavioural and electrophysiological studies in children with autism (e.g. Klin, Lin, Gorrindo, Ramsay, & Jones, 2009; Webb, Dawson, Bernier, & Panagiotides, 2006; see also McCleery, Stefanidou, & Graham, 2011).

Previous conflicting findings from behavioural, electrophysiological, and neuroimaging studies revealing either impaired processing of social stimuli (e.g., faces) or enhanced processing of non-social stimuli (e.g., objects) has led to a debate among research groups in the field, taking different perspectives with regard to the factors driving social-cognitive impairments in autism (McCleery, Stefanidou, & Graham, 2011). More specifically, there is a debate as to whether social-cognitive deficits in autism are driven by impairments in specific brain networks, including the amygdala

and the fusiform face area (e.g. Schultz, 2005; Schultz et al., 2003), decreased attention to social stimuli and engagement with others (e.g. Carver & Dawson, 2002; Dawson, Bernier, & Ring, 2012), or increased attention to / enhanced processing of non-social stimuli or local features as opposed to global processing (e.g. Jemel, Mottron, & Dawson, 2006; Mottron, 2011; Rondan & Deruelle, 2007; see also, McCleery, Stefanidou, & Graham, 2011). In addition, it has been recently suggested that the redistribution of brain function observed in individuals with ASD in previous neuroimaging studies, may, in fact, reflect superior performance, rather than impairment, in brain networks (Mottron, 2011).

1.2.3 Social attention in ASD

Although increased attention and sensitivity to different types of visual and auditory social stimuli, such as facial movements, eye-gaze, biological motion, and speech sounds has been previously documented by several studies in typically developing infants (e.g. Morton & Johnson, 1991; Rochat & Striano, 1999; Simion, Regolin, & Bulf, 2008; Vouloumanos et al., 2010; Vouloumanos & Werker, 2007), social attention in children with autism has been found to be impaired (Dawson, Bernier, & Ring, 2012).

Previous behavioural studies utilised either home videotapes or controlled experimental designs in order to investigate attention or preference for social cues in ASDs (e.g., Osterling, Dawson, & Munson, 2002; Pierce, Conant, Hazin, Stoner, & Desmond, 2011). For example, Baranek (1999) analysed home videos of 9- to 12-month old infants and reported that more prompts were needed to elicit a response to name, in infants who were later diagnosed with autism. Similarly, the analysis of home videos of

1-year old infants by Osterling, Dawson, and Munson (2002) revealed less frequent orienting to other people even when their name was called, in infants later diagnosed with an ASD, when compared with typically developing infants and infants with developmental disabilities. In addition, infants with autism were found to use gestures and look at objects held by another person less frequently than control infants (Osterling, Dawson, & Munson, 2002). Furthermore, Osterling and colleagues' (2002) findings replicated previous research using home video analysis, also revealing fewer responses to other people smiling in 8- to 10-month old infants with autism (Werner et al., 2000), and fewer joint attention behaviours, such as showing and pointing, in 1-year olds later diagnosed with ASD (Osterling & Dawson, 1994).

Impaired social attention in autism has also been documented by studies that employed behavioural experimental designs (e.g. Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Mosconi et al., 2009; see also Dawson, Bernier, & Ring, 2012). Dawson et al. (1998) employed a social orienting task, including social (e.g. clapping hands) and non-social (e.g. car horn) sounds, and reported that 4- to 6-year old children with ASD oriented less frequently to both types of stimuli, and especially to social sounds, relative to controls. These findings were replicated in a more recent study by Dawson et al. (2004), which revealed impaired social orienting and joint attention in 3-year old children with autism. Other studies comparing 20-month old toddlers with ASD with typically developing toddlers and toddlers with developmental delays, scored children's behaviour in more naturalistic play contexts and reported that toddlers with ASD oriented more frequently to objects than other people's activities in the environment (Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011; Swettenham et al., 1998). In addition, Mosconi et al. (2009) used the Social Orienting Continuum and

Response Scale (SOC-RS) in order to rate orienting to name, social referencing, social smiling, and joint attention during the administration of standardised activities of the Autism Diagnostic Observation Schedule (ADOS), and found that social referencing, orienting to name, and joint attention were impaired in children with autism at two years of age, whereas all four communicative behaviours were impaired in the same group of children at four years of age.

Recent studies using eye-tracking technology also examined orienting behaviour during visual preference and visual attention tasks, including both social and non-social stimuli, in children with autism (e.g. Klin, Jones, Schultz, Volkmar, & Cohen, 2002a; Pierce et al., 2011; Rice, Moriuchi, Jones, & Klin, 2012; see also, Dawson, Bernier, & Ring, 2012). Pierce and colleagues (2011) utilised a preferential looking paradigm, which presented a movie of human actions on one side and a video of moving geometric patterns on the other side. The authors reported that 14-month old toddlers with ASD showed a clear preference for the video of geometric patterns, which also predicted an ASD diagnosis, if they spent more than 69% of the testing time fixating on the non-social video (Pierce et al., 2011). In addition, other studies employing preferential looking paradigms used PLDs of biological motion, and examined preferential attention to biological motion relative to inverted PLDs or scrambled motion in toddlers and young children with autism (e.g. Annaz et al., 2012; Falck-Ytter, Rehnberg, & Bolte, 2013; Klin et al., 2009). The findings were consistent across the studies revealing less preferential attention to biological motion stimuli in the ASD groups when compared with controls (Annaz et al., 2012; Falck-Ytter, Rehnberg, & Bolte, 2013; Klin et al., 2009). In addition, two of the studies reported preferential attention to non-biological

motion or non-social audiovisual synchrony in toddlers and children with ASD (Annaz et al., 2012; Klin et al., 2009).

Other eye-tracking studies using visual attention tasks examined more specific looking patterns of children with autism, when shown videos of social and non-social scenes (e.g. Klin et al., 2002a; Shultz, Klin, & Jones, 2011). Klin et al. (2002a) showed adolescents and young adults with ASD clips of social scenes and found that they spent more time looking to objects relative to faces, compared to controls. In addition, longer fixation times on objects were found to predict higher levels of social impairment (Klin et al., 2002a). More recent findings by Rice et al. (2012) also revealed longer fixation times on body parts and objects relative to faces (eye and mouth region) presented in a social scene in school-aged children with ASD. Interestingly, Shultz, Klin, and Jones (2011) measured eye-blinking rates in 2-year old toddlers with autism or typical development while watching videos including both affective peer interactions (e.g. argument between boy and girl) and physical object movements (e.g., door closing). Toddlers with an ASD were found to blink less often while fixating on the non-social stimuli, whereas typically developing toddlers blinked less while fixating on the social scene (Shultz, Klin, & Jones, 2011). Greater blink inhibition during the non-social scene might reflect greater visual attention to non-social stimuli in toddlers with ASD (Shultz, Klin, & Jones, 2011).

Social attention atypicalities in children with ASD have also been observed in studies that have investigated auditory preference of speech relative to non-speech sounds (e.g. Klin, 1991; Kuhl, Coffey-Corina, Padden, & Dawson, 2005). For example, Klin (1991) used an audio feedback device with two choices: the mother's speech and a noise produced by voices in a busy canteen. The author recorded sound preferences in

4- to 6-year old children in their homes and found that children with autism showed a preference for either the non-speech sound or neither of the sound types, whereas typically developing children and developmentally delayed children preferred to listen to their mother's voice (Klin, 1991). These findings were replicated by a more recent study in 2- to 4-year old children with autism, who responded and oriented towards non-speech analogues more often relative to speech sounds during an auditory preference test (Kuhl et al., 2005).

Dawson and colleagues (2012) have argued that reduced attention or sensitivity to social cues and social engagement in autism may be associated with reduced sensitivity to social rewards. According to Dawson's (2008) *Social Motivation Hypothesis,* the dopamine system, which is the neural system associated with reward processing, with input from the amygdala, is responsible for the formation of reward value representations in the frontal cortex. The latter then mediates approach behaviour and engagement with the social world (Dawson, 2008). In addition, reduced attention to the social world may be associated with delays in social and language development; for example, reduced interest and attention to other people's eye-gaze or faces may have further negative downstream consequences for the development of social engagement and joint attention, which have also been suggested to be precursors for language development and Theory of Mind (ToM) (Charman et al., 2000; Dawson, Bernier, & Ring, 2012; Toth et al., 2006). Moreover, decreased attention to other peoples' actions, or difficulties distinguishing biological from non-biological motion, may have a negative impact on the comprehension of other people's actions and mental states, and the associated development of "mentalizing" skills, which are known to be delayed in individuals with ASD (e.g. Baron-Cohen, Leslie, & Frith, 1985; Frith & Frith, 1999).

1.2.4 Behavioural evidence for biological motion and action recognition and perception in ASD

1.2.4.1 Behavioural evidence for action understanding and perception in ASD

Behavioural research revealing deficits in social attention (e.g. Dawson et al., 1998; Dawson et al., 2004; Klin et al., 2009; Mosconi et al., 2009; see also, Dawson, Bernier, & Ring, 2012), and preference for objects or other non-social stimuli over faces, other people's actions, and speech in young children and adolescents with autism (e.g. Klin, 1991; Klin et al., 2002a; Kuhl et al., 2005; Pierce et al., 2011; Shic et al., 2011; see also, Dawson, Bernier, & Ring, 2012; Klin, Jones, Schultz, Volkmar, & Cohen, 2002b) has given rise to the investigation of the detection and perception of social stimuli, such as faces, eye-gaze, biological motion and other people's actions, by individuals with autism. For example, recent research studies have reported that individuals with ASD exhibit atypical scanning of faces, focusing more on the mouth or other external facial features (e.g., cheeks, forehead, hair) relative to the eye region (e.g. Chawarska & Shic, 2009; Jones, Carr, & Klin, 2008; Klin et al., 2002a). In addition, other studies have revealed impaired perception and discrimination of faces (e.g. Behrmann et al., 2006; van der Geest, Kemner, Verbaten, & Van Engeland, 2002;), and atypical detection and perception of eye-gaze, which individuals with autism have been found to be less responsive to or oversensitive to, compared to controls (e.g. Leekam, Lopez, & Moore, 2000; Senju et al., 2004; Vivanti et al., 2011). In addition, studies of biological motion and action perception in individuals with ASD have reported difficulties in the perception and recognition of biological motion (e.g. Centelles, Assaiante, Etchegoyhen, Bouvard, & Schmitz, 2013; Freitag et al., 2008; Parron et al., 2008; see also, Kaiser & Pelphrey, 2012), as well as in the understanding of other

people's actions and intentions (e.g. Cossu et al., 2012; Zalla, Labruyere, & Georgieff, 2013), which will be discussed further below.

Difficulties in the comprehension and production of body actions and gestures (e.g., pointing, facial gestures, body movements) as well as in motor imitation have been documented by several studies in children and adolescents with ASD (e.g. Cossu et al., 2012; Ingersoll, 2008a; Mundy, Sigman, Ungerer, & Sherman, 1986; Rogers, Hepburn, Stackhouse, & Wehner, 2003; Stone, Ousley, & Littleford, 1997; Vanvuchelen, Roeyers, & de Weerdt, 2007). More specifically, some of the most prominent imitation delays or deficits in autism include procedural imitation (Vanvuchelen, Roeyers, & de Weerdt, 2010), imitation of non-meaningful gestures (e.g. Vanvuchelen, Roeyers, & de Weerdt, 2007), and spontaneous imitation in naturalistic contexts compared with structured-elicited imitation (Ingersoll, 2008a). In a recent systematic review, Vanvuchelen, Van Schuerbeeck, Roeyers, and De Weerdt (2013) discussed several different hypotheses about imitation deficits in ASD, including the social attention and the biological motion preference hypotheses, and argued that the relationship between social attentiveness or biological motion preference and performance on both structured and spontaneous imitation tasks needs further investigation. Interestingly, two recent studies examined attention patterns and joint attention behaviours during imitation tasks in children and adolescents with ASD, and revealed decreased attention to the examiner (Hobson & Hobson, 2007; Vivanti et al., 2008), as well as increased attention to objects that the examiner acted upon, and fewer "sharing looks", in the ASD groups (Hobson & Hobson, 2007). These findings provide additional evidence for the role of social attention in the comprehension of other people's actions, joint attention, and imitation ability, which has both a learning and a

social function, and plays a key role in communication and social development (Dawson, Bernier, & Ring, 2012; Ingersoll, 2008b).

Other behavioural research studies have also investigated the recognition and perception of pantomimes, goal-directed actions and sequences of actions in children and adolescents diagnosed with an ASD (e.g. Cossu et al., 2012; Vivanti et al., 2011; Zalla, Labruyere, & Georgieff, 2006). Cossu et al. (2012) reported that school-aged children with ASD performed significantly worse than typically developing children on a pantomime comprehension task. In addition, Zalla, Labruyere, and Georgieff (2006) employed a sequencing task and found that adolescents with autism had difficulties in arranging pictures of actions on objects in the correct order to create a reasonable event in pictures. The authors argued that this type of difficulty in sequencing actions might be associated with deficits in understanding others' actions and behaviour (Zalla, Labruyere, & Georgieff, 2006). In a more recent study, the same research group compared adolescents with ASD with typically developing individuals and individuals with learning disabilities on an event detection and action segmentation task, in order to examine their ability to distinguish single meaningful events or actions within a familiar sequence of actions (Zalla, Labruyere, & Georgieff, 2013). Their findings revealed that the ASD group was less accurate than typically developing individuals at event detection, and that this reduced accuracy was also associated with mentalizing skills (Zalla, Labruyere, & Georgieff, 2013).

Other studies investigating goal-directed action perception in autism have revealed deficits in understanding and predicting goals and intentions of other people's actions (Falck-Ytter, Fernell, Hedvall, von Hofsten, & Gillberg, 2012; Zalla, Labruyère, Clément, & Georgieff, 2010). For example, in a recent research study, children with

autism were found to have difficulties in interpreting another person's head turn towards an object as an action showing intention to use the object (Vivanti et al., 2011). In addition, Falck-Ytter and colleagues (2012) employed eye-tracking measures in order to record children's eye movements while watching videos of an actor looking or pointing to a toy. Unlike their previous findings using a corneal reflection technique (Flack-Ytter, 2010), the authors demonstrated that children with autism looked at the toy less than the comparison group (Falck-Ytter et al., 2012). These results support previous findings revealing action understanding and joint attention impairments in ASD (e.g., Charman, 1998; Dawson et al., 2002). Moreover, Stoit et al. (2011) tested children's with ASD ability to predict another person's action or response during a computerised bar-balancing task and reported that, unlike typically developing children, participants with ASD had difficulties in predicting their partners' actions and in coordinating their responses. On the other hand, in a study utilising a behavioural task of incomplete actions, children and adolescents with autism were also found to encounter difficulties in understanding and predicting the goal of incomplete familiar or unfamiliar actions, when compared with groups of typically developing children and children with developmental delays (Zalla et al., 2010). However, Boria and colleagues (2009) did not find any differences between the ASD and comparison groups, when they asked them to name the actions produced by hand-object interactions shown in pictures and explain why they were performed. Interestingly, though, that was the case only when children with ASD relied on the object's standard use; when they had to rely only on the motor aspects of the action, their understanding of the intention of the actions was impaired (Boria et al., 2009).

1.2.4.2 Behavioural evidence for biological motion recognition and perception in ASD

As previously mentioned, two-year old toddlers with ASD were found to show greater preference for non-social audiovisual synchronies relative to biological motion in PLDs (Klin et al., 2009). This attentional preference at such an early age may be associated with reduced sensitivity to, and impaired perception of, biological motion and human actions previously reported in individuals with autism (see also, Kaiser & Pelphrey, 2012). Previous studies of biological motion perception have revealed impairments in the detection and recognition of biological motion depicted in PLDs in children diagnosed with ASD (e.g. Blake, Turner, Smoski, Pozdol, & Stone, 2003; Centelles et al., 2013). Blake et al. (2003) utilised PLDs of biological motion and scrambled incoherent motion and examined whether school-aged children with autism had more difficulties in recognizing biological motion, when compared with typically developing children. Although no group differences were found on the scrambled motion task, children with autism performed significantly worse than controls on the biological motion task (Blake et al., 2003). In a more recent study, Koldewyn, Whitney, and Rivera (2010) employed a psychophysical task including biological motion, coherent motion, and coherent forms, and measured detection thresholds in adolescents with ASD, and age and ID matched control participants. In accordance with the findings of Blake et al. (2003), their results revealed worse performance on the biological motion processing task for the ASD group (see also Koldewyn, Whitney, & Rivera, 2011). In addition, Centelles and colleagues (2013) showed school-aged children PLDs of figures interacting with each other or PLDs involving no social engagement, and demonstrated that the autism group exhibited more difficulties in recognizing both PLD types, and especially the social interaction ones, when compared with age and non-verbal ability

matched typically developing children. These findings replicated the authors' previous findings revealing that children with ASD performed less efficiently than controls on a forced-choice task including PLDs of conventional gestures, emotional situations, and social scenes from games (Centelles et al., 2012). Finally, in another recent study, Swettenham et al. (2012) employed a spatial attention task with a PLD depicting a pointing gesture or a scrambled version of the gesture, orienting towards the location of a validly or an invalidly cued target. Unlike typically developing children, school-aged children with ASD did not manage to locate the validly cued targets faster than the invalidly cued ones.

The aforementioned research findings in children with autism are consistent with previous findings of biological motion perception in adults with ASD. More specifically, adults with ASD have been found to exhibit difficulties in detecting and recognizing both biological motion and emotions in PLDs (Atkinson, 2009; Nackaerts et al., 2012). Additionally, recent studies utilising PLDs of both biological (e.g. moving hand) and non-biological (e.g. falling ball) motion have demonstrated that, unlike neurotypical adults, adults with ASD did not show higher sensitivity to biological motion relative to non-biological motion displays (Cook, Saygin, Swain, & Blakemore 2009; Kaiser, Delmolino, Tanaka, & Shiffrar, 2010a). Interestingly, another study by Freitag et al. (2008) in adolescents and adults with ASD revealed intact biological motion recognition but longer reaction times for both the biological and scrambled motion recognition tasks for the ASD group, when compared with age, gender and IQ matched control participants. According to the authors, these results may reflect a greater cognitive effort by individuals with ASD to categorize the displays (Freitag et al., 2008).

However, other studies that examined biological motion and emotion recognition in PLDs in children and adults with autism have shown deficits only in emotion detection (Hubert et al., 2006; Moore, Hobson, & Lee, 1997; Parron et al., 2008), with biological motion perception remaining intact in the autism groups in some of the studies (Murphy, Brady, Fitzgerald, & Troje, 2009; Saygin, Cook, & Blakemore, 2010). Kaiser and Pelphrey (2012) argued that these conflicting findings might reflect changes and improvements in the course of socio-cognitive development through adulthood, differences in experience with actions, or cognitive ability across groups, which has also been found to be associated with biological motion perception in individuals with ASD (Rutherford & Troje, 2012).

1.2.5 Social processing in ASD- Evidence from neuroimaging and electrophysiological studies

In order to establish the neurophysiological mechanisms underlying the behavioural phenotype of autism spectrum disorders, several research groups have employed neuroscientific measures, such as neuroimaging and electrophysiological techniques, in order to investigate brain networks and functions associated with the neural processing of static and dynamic social stimuli. Notably, numerous studies of social processing in autism have revealed atypical processing of faces or facial expressions and emotions (e.g. Dawson et al., 2002; Dawson et al., 2004; Pelphrey, Morris, McCarthy, & LaBar, 2007; Pierce, Müller, Ambrose, Allen, & Courchesne, 2001; Pierce & Recay, 2008; Webb et al., 2006; Webb et al., 2011; see also, Jemel, Mottron, & Dawson, 2006; Schultz, 2005), eye gaze (e.g. Grice et al., 2005; Pelphrey, Morris, & McCarthy, 2005), biological motion (e.g. Castelli, Frith, Happé, & Frith,

2002; Coldewyn, Whitney, & Rivera, 2011; Freitag et al., 2008; Herrington et al., 2007; Kaiser et al., 2010a; see also, Kaiser & Pelphrey, 2012), body actions (e.g. Bastiaansen et al., 2011; Bernier, Dawson, Webb, & Murias, 2007; Cattaneo et al., 2007; Dapretto et al., 2005; Enticott et al., 2012; Martineau, Andersson, Barthélémy, Cottier, & Destrieux, 2010; Oberman et al., 2005; Oberman, Ramachandran, & Pineda, 2008; see also, Oberman et al., 2013), and speech (e.g. Ceponiene et al., 2003; Eyler, Pierce, & Courchesne, 2012; Harris et al., 2006; Lepisto et al., 2005, Lepisto et al., 2006, Lepisto, Nieminen-von Wendt, von Wendt, Näätänen, & Kujala, 2007; Redcay & Courchesne, 2008) in individuals with ASD. For example, in recent ERP studies, unlike typically developing children, young children with autism failed to show differential neural responses to familiar versus unfamiliar faces, but they showed enhanced responses to objects (Dawson et al., 2002; Webb at al., 2006). In addition, fMRI findings in older, school-aged children with autism revealed similar fusiform activity in response to their mother's face and the faces of familiar or unfamiliar children across the groups, but significantly less activity in response to strangers' faces (Pierce & Redcay, 2008). Similarly, other studies employing EEG and fMRI techniques have provided evidence for both impaired and intact neural mechanisms for the perceptual processing of biological motion and human actions in children with ASD (e.g. Dapretto et al., 2005; Kaiser et al., 2010a; Koldewyn, Whitney and Rivera, 2011; Oberman, Ramachandran, & Pineda, 2008; Raeymaekers, Wiersema, & Roeyers, 2009), which will be discussed further below.

1.2.5.1 Neural processing of biological motion in ASD

Previous neuroimaging studies, examining biological motion processing in adults with autism, have consistently reported impaired neural networks and atypical processing of biological motion in ASD groups (e.g. Castelli, et al., 2002; Freitag et al., 2008; Herrington et al., 2007). Castelli et al. (2002) showed adults with ASD and neurotypical controls animations of triangles, which were either moving in a random way, or in a goal directed way, or they were interacting with each other implying intentions. The ASD group made more mistakes describing the interactive animations during the third condition, which required mentalizing skills and elicited less activity in the mentalizing neural network, including the STS, the temporal poles and the medial prefrontal cortex, in the ASD group relative to the comparison group (Catelli et al., 2002). In addition, although the extrastriate cortex was activated in both groups, its functional connectivity with the STS at the temporo-parietal junction was reduced in the autism group (Castelli et al., 2002). Similarly, McKay et al. (2012) utilised PLDs of canonical and scrambled biological motion and, based on their findings of differential activation of neural networks in the ASD and comparison groups, proposed that temporal and parietal regions were underconnected in the ASD group. In addition, other fMRI studies revealed reduced activation of the temporal regions and the human analogue of MT+/V5 (Herrington et al., 2007), as well as hypoactivation of the somatosensory cortex, the right inferior parietal lobule (IPL) and the right middle temporal gyrus (MTG) (Freitag et al., 2008) in response to PLD walkers in the ASD groups.

Research findings from biological motion processing studies in children and adolescents with ASD have extended previous research work in adults. Koldewyn,

Whitney and Rivera (2011) used biological and coherent motion displays and found that biological motion elicited reduced activity over frontal and parietal regions, as well as over the posterior STS in a group of adolescents with ASD relative to typically developing participants. Koldewyn and colleagues' (2011) findings supported previous research suggesting an almost intact coherent motion processing mechanism (e.g. Vandenbroucke et al., 2008; White et al., 2006). In addition, in a recent fMRI study in 4- to 17-year old children and adolescents, Kaiser et al. (2010b) identified "state", "trait" and "compensatory" activity in children with ASD and their unaffected siblings. They argued that "state" activity refers to brain activity and mechanisms that are unique to ASD, whereas "trait" activity refers to brain activity that is common in children with ASD and their unaffected siblings (Kaiser et al., 2010b). On the other hand, "compensatory" activity reflects brain activity and the additional brain mechanisms or areas recruited, which might compensate for the genetic risk for autism and are unique to unaffected siblings of children with ASD (Kaiser et al., 2010; see also, Kaiser & Pelphrey, 2012, for a review). The "state" activity was observed over a brain network including the right posterior STS, the ventromedial and ventrolateral prefrontal cortex, the right amygdala and the bilateral fusiform gyri, whereas "trait" mechanisms included the bilateral fusiform gyri, the right inferior temporal gyrus and the left dorsolateral prefrontal gyrus (Kaiser et al., 2010b). Finally, the right posterior STS and the ventromedial prefrontal cortex were activated only in unaffected siblings, reflecting "compensatory" activity (Kaiser et al., 2010b). These neuroimaging findings provide evidence for a neuroendophenotype with respect to biological motion processing in autism (Kaiser et al., 2010b; Kaiser & Pelphrey, 2012).

On the other hand, in a more recent ERP study by Kroger et al. (2013), 6- to 15-year old children and adolescents with ASDs presented with a differential neural activity pattern in response to biological and random motion, when compared with typically developing controls. This was reflected in two early processing components (P100, N200), with P100 amplitude being reduced to both types of motion over the occipital sites and N200 being atypically lateralized in the autism group. In addition, a later slow deflection (P400) over the centro-parietal channels was found to be smaller in the ASD group (Kroger et al., 2013). The authors argued that the latter reflects top-down processes and possibly an impaired biological motion processing mechanism in ASD (Kroger et al., 2013).

1.2.5.2 Neural processing of visual action stimuli in ASD

Numerous research groups have also focused on the investigation of body action processing in autism (e.g. Bernier et al., 2007; Martineau, Cochin, Magne, & Barthelemy, 2008; Oberman et al., 2005; see also Hamilton, 2013, for a review). The specialised brain system that has been primarily thought to underlie the perception and comprehension of body actions is the mirror neuron system (MNS; Rizzolatti et al., 2001) (see also, *Chapter 1, Section 1.2.1*), which has been found to be dysfunctional in individuals with ASD (e.g. Martineau et al., 2008; Oberman et al., 2005; Oberman et al., 2013).

Oberman et al. (2005) investigated MNS function in individuals with ASD, by recording the power of the mu rhythm, while child and adult participants watched videos of body (e.g. a moving hand) or non-body actions (e.g. a bouncing ball). Their findings revealed a mirror neuron dysfunction in individuals with ASD when compared

with control participants, as their mu rhythm was not suppressed while watching the body action videos. This finding was replicated by Bernier et al. (2007), who demonstrated that mu rhythm in adults with ASD was significantly attenuated during hand action execution, but not during the observation of a grasping action. The authors also found that mirror neuron activity was highly correlated with body action imitation skills, and especially imitation of facial expressions, in adults with ASD (Bernier et al., 2007). In addition, Oberman, Ramachandran, and Pineda (2008) showed mu wave suppression in 8- to 12-year old children with ASD while observing hand actions (open/close), but only when the actions were performed by familiar individuals. Moreover, another EEG study by Martineau et al. (2008) revealed a lack of EEG desynchronisation in theta band 1 over the motor cortex and the frontal- temporal regions in response to leg movement videos in 5- to 7-year old children with autism, when compared with age and gender matched controls.

A dysfunctional MNS was also found in both children and adults with autism by research groups utilising magnetoencephalography (MEG) (e.g. Honaga et al., 2010) and fMRI techniques (e.g. Bastiaansen et al., 2011; Dapretto et al., 2005; Martineau et al., 2010). Honaga et al. (2010) reported reduced post-movement beta rebound (PMBR) in the sensorimotor and premotor cortices, the superior temporal gyrus and the prefrontal cortex during the observation of object-related hand actions in adults with ASD relative to controls. In addition, an fMRI study in 12-year old children with ASD revealed reduced activity in the inferior frontal gyrus during the observation and imitation of facial emotional expressions (Dapretto et al., 2005). Importantly, mirror neuron activity was found to be negatively correlated with the children's scores on the social subscales of the Autism Diagnostic Observation Scales-Generic (ADOS-G) and

the Autism Diagnostic Interview-Revised (ADI-R). These findings of atypical mirror neuron activity in school-aged children and adolescents with autism were also replicated by fMRI studies in adults (Bastiaansen et al., 2011; Martineau et al., 2010), but in the opposite direction. The latter presented with increased inferior frontal gyrus activity during the observation of hand movements (Martineau et al., 2010) and dynamic facial expressions (Bastiaansen et al., 2011) when compared with neurotypical individuals.

Other studies supporting the "broken mirror" theory in autism employed transcranial magnetic stimulation (TMS) and motor evoked potentials (MEPs) in order to measure primary motor cortex (M1) excitability during the observation of meaningless finger movements (Theoret et al., 2005) and goal-directed hand actions involving an object (Enticott et al. 2012) in adults with ASD. During both studies TMS was administered to the M1 and MEPs were recorded from the first dorsal interosseus (FDI). Theoret et al. (2005) findings revealed that participants with ASD exhibited MEP facilitation, only when the finger movement was towards themselves (as if it belonged to someone else); on the other hand, the egocentric view condition elicited no muscle-specific enhancement in the ASD group, as opposed to the comparison group. In addition, in a larger sample, Enticott and colleagues (2012) found that adults with ASD showed reduced motor corticospinal excitability (CSE) during the observation of a transitive grasping action, when compared with neurotypical adults, who exhibited MEP enhancement during the observation of a transitive hand action relative to a static hand. The impaired primary motor cortex function revealed by Theoret et al. (2005) and Enticott et al. (2012) in adults with ASD might reflect a dysfunctional mirror neuron system in autism (see also, Hamilton, 2013).

In addition, another study using electromyography (EMG), recorded EMG activity from the mylohyoid (MH) muscle during the execution and observation of a grasping action in 5- to 9-year old children with autism and typically developing controls (Cattaneo et al., 2007). The actions presented to the children included: a) a hand action grasping food from a plate, bringing it to the mouth and eating it, and b) a hand action grasping a piece of paper from a plate and placing it into a container. EMG findings revealed that during the execution of the action, children with autism did not activate the MH until after the grasping phase, as opposed to typically developing children who showed MH activity from the "reaching the food/paper" phase of the action. In addition, the ASD group showed no MH activation during action observation, as opposed to controls, who showed increased muscular activity during all phases of the observed action. The authors argued that the MNS relies on an action-chain mechanism with mirror properties, which seems to be impaired in children with autism (Cattaneo et al., 2007). This mechanism is activated during the observation of an initial motor act of an action and is responsible for the understanding of the goal of an action from the first phase of action observation in neurotypical individuals (Catteneo et al., 2007).

However, the "broken" mirror theory of autism has been questioned by recent studies employing EEG (Fan, Decety, Yang, Liu, & Cheng, 2010; Raeymaekers, Wiersema & Roeyers, 2009), EMG (Pascolo & Cattarinussi, 2012), and fMRI techniques (Dinstein et al., 2010; Grezes, Wicker, Berthoz, & De Gelder, 2009; Marsh & Hamilton, 2011; Schulte-Ruhter et al., 2011; see also, Hamilton, 2013, for a review), which revealed an intact mirror neuron function in ASD groups. For example, Fan and colleagues (2010) investigated mu rhythm suppression during the execution and observation of hand actions versus a moving dot in adolescents and young adults with

ASD, but they did not find any differences in sensorimotor cortex activity between the ASD and comparison groups. Similarly, no differences between groups of children with autism and typically developing children were found by Raeymaekers, Wiersema and Roeyers (2009), who reported, though, a correlation between the degree of mu suppression and age, with children younger than 11 years of age showing less mu wave suppression. This notion, however, was not supported by a more recent examination of a large cohort of EEG mu rhythm data pooled across several studies, which suggested that visual MNS impairment is present from an early age in autism and that it does not improve with age (Oberman et al., 2013).

The aforementioned mixed findings regarding the MNS function in individuals with ASD might be associated with the complex clinical picture and heterogeneity of autism (see also Pelphrey, Shultz, Hudac, & Vander Wyk, 2011), as well as differences in sample sizes and experimental designs used in previous studies. In addition, Hamilton (2013) suggested an alternative model, the "social top-down response modulation model", instead of the "broken mirror" model, in order to provide an alternative account for the functioning of the mirror neuron system in autism and the previous mixed literature. According to this model, information is sent from the visual systems to the parietal, premotor and motor cortices and it is then filtered through a top-down modulation process, possibly originating from the prefrontal or frontal cortex (Hamilton, 2013). This means that the visuomotor stream may be modulated by social cues, and more specifically by past experience of observed actions (Hamilton, 2013). Hamilton's (2013) model highlights the role of top-down processes and previous social experience, and might provide a reasonable explanation for previous EEG/ERP and FMRI findings revealing differential neural activity to familiar versus unfamiliar stimuli

(e.g. Oberman, Ramachandran, & Pineda, 2008; Pierce & Redcay, 2008). Moreover, such a neural processing model may explain impaired social processing mechanisms in autism, as a result of reduced social attention during infancy and childhood (see also, Dawson, Bernier, & Ring, 2012). However, this model was only recently described and suggested, and further research is needed to examine it in more detail.

1.2.5.3 Neural processing of auditory action stimuli and speech in ASD

To our knowledge, no auditory action processing studies have been conducted in children or adults with ASD to date. However, there is some preliminary evidence for atypical processing of non-speech vocalizations (e.g. laughing, crying, yawning) in 4- to 6-month old infants who are at risk for autism, when compared with low-risk infants (Lloyd-Fox et al., 2013), which will be discussed further below.

Several electrophysiological (e.g. Ceponiene et al., 2003; Coffey-Corina, Padden, & Kuhl, 2008; Kuhl et al., 2005; Lepisto et al., 2005; Lepisto et al., 2007; Lepisto et al., 2006; Whitehouse & Bishop, 2008) and neuroimaging (e.g. Eyler, Pierce, & Courchesne, 2012; Harris et al., 2006; Lai, Pantazatos, Schneider, & Hirsch, 2012; Redcay & Courchesne, 2008) studies have revealed atypical discrimination and perceptual processing of speech and language in children and adults with ASD. Interestingly, the neural processing of speech integrated with beat gestures has also been found to be atypical in autism, eliciting greater activity in the visual regions in children with ASD, as opposed to the secondary auditory cortices, which were activated in typically developing children (Hubbard et al., 2012).

Results from recent fMRI studies in toddlers and children with autism have revealed reduced activation of the left hemisphere (e.g. Eyler, Pierce, & Courchesne,

2012; Lai et al., 2012) and greater activation of right frontal and temporal regions in response to speech sounds (e.g. Eyler, Pierce, & Courchesne, 2012; Redcay & Courchesne, 2008). In addition, a rightward hemispheric asymmetry (Gage et al., 2009), and a weaker interhemispheric functional connectivity in cortical areas subserving language processing, including the inferior frontal gyrus (IFG) and the superior temporal gyrus (STG) (Dinstein et al., 2011), have also been documented in children with ASD. Notably, a recent study employing resting-state functional MRI revealed that the posterior STS, which has been found to be involved in human voice processing, is under-connected to brain areas associated with emotion and reward processing, including the amygdala, and the orbitofrontal and prefrontal cortices, in children with ASD (Abrams et al., 2013). These findings support the *Social Motivation Hypothesis* (see *Section 1.2.3*), which predicts that impaired reward systems may underlie reduced social attention and deficient perceptual processing of social stimuli, such as human actions and speech in autism (Abrams et al., 2013; Dawson, Bernier, & Ring, 2012).

On the other hand, EEG/ERP studies have investigated sound discrimination and orienting to speech in children and adults with autism, by utilising oddball ERP paradigms, and measuring both early sensory processing stages (P1, N1), as well as later stages of cognitive processing, reflecting the recognition and classification of auditory stimuli (MMN, P3a, P3b, N400) (e.g. Ceponiene et al., 2003; Kuhl et al., 2005; Lepisto et al., 2005; Lepisto et al., 2007; Lepisto et al., 2006; Whitehouse & Bishop, 2008). More specifically, smaller P1 responses to speech stimuli (e.g. Ceponiene et al., 2003; Lepisto et al., 2005; Russo, Zecker, Trommer, Chen, & Kraus, 2009), as well as delayed P1 latencies (Russo et al., 2009) were found in ASD groups relative to controls. In addition, another study investigating neural responses to emotional voices found

delayed N1 responses to angry voices, embedded in a stream of neutral voice stimuli, in children with Asperger's Syndrome (Korpilahti et al., 2007; see also, O'Connor, 2012).

Findings from the aforementioned studies have also revealed smaller MMN and P3a amplitudes to pitch changes in speech stimuli (vowels) in children with autism relative to typically developing children (Ceponiene et al., 2003; see also Kujala, Lepisto, & Naatanen, 2013; Lepisto et al., 2005; Lepisto et al., 2006). In addition, in a study by Kuhl et al. (2005), which revealed enhanced behavioural orienting to non-speech sounds in young children with autism (see also, *Section 1.2.3*), the latter showed reduced MMNs to deviant syllables embedded in a stream of other standard syllables. Notably, this atypical neural activity pattern was present only in children with autism, who also showed a preference for non-speech sounds (Kuhl et al., 2005). Reduced P3b amplitudes to speech sounds in individuals with autism were also observed in studies using either deviant speech stimuli embedded in streams of standard speech sounds, or rare phonemes embedded in streams of non-speech sounds (chord) (Courchesne, Lincoln, Kilman, & Galambos, 1985; Dawson, Finley, Phillips, Galpert, & Lewy, 1988; see also, O'Connor, 2012). However, a more recent study by Lepisto et al. (2007) reported larger P3a amplitudes to non-speech changes and smaller P3a amplitudes to speech changes in adults with Asperger's Syndrome relative to controls. Moreover, Whitehouse and Bishop (2008) employed a different oddball paradigm, including speech and non-speech sounds in the same stream. Hence, in streams of standard speech sounds (vowels), the rare, deviant stimulus was a non-speech sound (complex tone), whereas in streams of non-speech sounds, the rare, deviant stimulus was a speech sound (vowel). The ERP findings revealed that children with autism exhibited reduced P3a responses to rare, non-speech stimuli, which, however, were increased when only high-

functioning children who paid attention and detected the targets, were included in the analysis (Whitehouse & Bishop, 2008; see also, Kujala, Lepisto, & Naatanen, 2013, for a review). The authors argued that these group differences may be associated with impaired "top-down" processing of repeated streams of standard speech sounds (Whitehouse & Bishop, 2008).

At a later stage of perceptual processing, N400 responses to speech stimuli have also been found to be diminished in children with ASD, relative to controls, in studies utilising oddball paradigms (Lepisto et al., 2005; Lepisto et al., 2006). Moreover, studies employing semantic match-mismatch paradigms have revealed reduced or absent N400 amplitudes in response to mismatching picture-word pairs in children with ASD (McCleery et al., 2010) and in response to semantically incongruent sentences in adults with ASD (Fishman, Yam, Bellugi, Lincoln, & Mills, 2011). Similarly, Dunn and Bates (2005) showed that, unlike typically developing children, school-aged children with autism failed to exhibit different N400 responses to irrelevant relative to target words from a specific semantic category, during a word identification task (see also, O'Connor, 2012).

These findings provide evidence for deficient speech processing brain mechanisms in individuals with ASD, which might potentially also be associated with social attention, and, more specifically, biological motion and action processing in autism. This notion may be consistent with previous suggestions that language and gesture processing are mediated by shared brain mechanisms and networks (e.g. Bates & Dick, 2002), including the STS, which has been associated with both language and social functions, and has been found to be neuroanatomically and neurofunctionally impaired in autism (Redcay, 2008). Furthermore, some of the aforementioned findings

also reveal an atypical imbalance of social (speech) versus non-social (non-speech) processing (e.g. Lepisto et al., 2007), which is consistent with findings of previous studies of face processing (Webb et al., 2006), biological motion detection (e.g. Klin et al., 2009), and social attention in autism (e.g. Klin et al., 2002a; Pierce et al., 2011).

1.2.6 Social versus non-social processing in ASD

Previous conflicting findings revealing both normal and atypical neural responses to social stimuli in autism may reflect a different perceptual processing strategy or a natural tendency to attend to local features over global information, rather than a perceptual impairment, as previously suggested (Jemel, Mottron, & Dawson, 2006; see also, McCleery, Stefanidou, & Graham, 2011). This notion, combined with findings from face and eye gaze processing studies showing similar neural responses in young ASD groups and developmentally delayed or younger groups (Grice et al., 2005; Webb et al., 2011), and impaired neural responses only to unfamiliar faces or unfamiliar actors performing an action (e.g. Oberman, Ramachandran, & Pineda, 2008; Pierce & Redcay, 2008) in children with ASD, may reflect an attentional imbalance between social and non-social cues in autism. More specifically, reduced attention to social stimuli, such as faces, eye-gaze, and voices (see Dawson, Bernier, & Ring, 2012, for a review), and/or preference for non-social stimuli, such as objects over faces or others' activities (e.g. Shic et al., 2011), non-biological motion over biological motion (e.g. Klin et al., 2009), and non-speech sounds over speech sounds (Kuhl et al., 2005) by individuals with ASD, may be associated with impaired social processing (e.g. Kaiser et al., 2010a; Oberman et al., 2005), or enhanced non-social neural processing, respectively (e.g. Lepisto et al., 2007; Webb et al., 2006). However, this attentional preference and perceptual

processing style may change through development and with experience with social interaction and social cues, such as faces and other people's actions, providing a potential explanation for conflicting findings sometimes revealing typical responses to social stimuli, such as faces, in adults with ASDs (e.g. Bailey, Braeutigam, Jousmäki, & Swithenby, 2005).

1.3 The Broader Autism Phenotype – Evidence for social processing from studies in infant and toddler siblings at risk for ASD

1.3.1 Introduction

Kanner's (1943) suggestion that autism is present from infancy and that it reflects a biological impairment, in combination with a considerable increase in prevalence of autism spectrum disorders over the last two decades (close to 60 per 10000) (e.g. Baio, 2012; Baird et al., 2006; Bertrand et al., 2001; Chakrabarti & Fombonne, 2005), led to the investigation of early signs of the disorder through the retrospective analysis of home videos (see *Section 1.2*; see also, Rogers, 2009). However, the lack of experimental control inherent in this method, along with the need for longitudinal studies including larger samples, has given rise to the study of infant siblings of children diagnosed with ASD, who have been found to be at higher risk of developing the disorder (Rogers, 2009).

The recurrence rate of autism in younger siblings of children with ASD has been found to range from 2% to 9% by previous studies (Newschaffer et al., 2012), however the Baby Siblings Research Consortium Study recently revealed a higher recurrence rate of 18,7% in a group of 664 infants, who were followed from infancy to 3 years

(Ozonoff et al., 2011). In fact, familial risk studies (e.g. Bailey, Palferman, Heavey, & Le Couteur, 1998; Bolton, Pickles, Murphy, & Rutter, 1998; Piven, Palmer, Jacobi, Childress, & Arndt, 1997a; Ritvo et al., 1989), twin studies (e.g. Bailey et al., 1995; Folstein & Rutter, 1977; Steffenburg et al., 1989), studies of genetic disorders presenting with an ASD behavioural phenotype, such as Fragile X Syndrome and Tuberous Sclerosis Complex (e.g. Brown et al., 1986; Smalley, 1998; Steffenburg et al., 1996), as well as studies employing genomic analysis methods (Anney et al., 2010; Bucan et al., 2009; Miller et al., 2009), have provided evidence for a relatively strong genetic liability of autism (see also, Geschwind, 2011; Newschaffer et al., 2012). However, recent findings revealing over 100 candidate genes, likely interacting with each other in order to contribute to the development of mechanisms that are deficient in ASD, has elucidated the high likelihood that the understanding of etiological mechanisms of ASD will be highly complex (Newschaffer et al., 2012). In addition, in their review, Happe and Ronald (2008) suggested that the autism "triad of impairments" is "fractionable" and that independent genes may be associated with different social or non-social aspects of autism. These findings, along with the notion that gene-environment interaction also plays a key role in the etiology of ASD (Hallmayer et al., 2011), demand the use of more sophisticated methods by genomic studies, as well as the development of large longitudinal studies of ASD infant siblings (Newschaffer et al., 2012; Rogers, 2009). The focus of the current literature review will be on the Broader Autism Phenotype (BAP), as reflected in cognitive development, social and communication skills, and social cognition in ASD family members, and especially in high-risk infant and toddler siblings of individuals with ASD.

1.3.2. The Broader Autism Phenotype (BAP) – Evidence from behavioural and neuroimaging research in ASD family members

The genetic liability of autism spectrum disorders has been investigated through numerous studies exploring the Broader Autism Phenotype (BAP), which reflects the subclinical, autism-related behavioural, cognitive, and neural processing traits, including both enhancements and deficits, in relatives of individuals with ASD (e.g. Rogers, 2009).

The behavioural phenotype of autism includes core autistic traits, such as language and communication impairments, social deficits, and repetitive behaviours, as well as behavioural difficulties and psychiatric disorders associated with ASD. There have been several studies indicating impaired narrative performance (Landa, Folstein, & Isaacs, 1991), pragmatic language deficits (Landa et al.,1992; Piven et al., 1997b), early language difficulties (Folstein et al., 1999), and communication deficits (Bolton et al, 1994; Pickles et al., 2000) in parents as well as second degree relatives (Pickles et al., 2000) of children with autism when compared with parents of children with Down Syndrome. Communication and social deficits have also been found in ASD parents, when compared with parents of typically developing children, as they scored higher on the Autism Spectrum Quotient, a questionnaire developed to screen for autistic traits of the BAP in families of individuals with autism (Bishop et al., 2004). In addition, other research findings have revealed impaired phonological processing and poorer vocabulary abilities in brothers of girls with autism (Plumet, Goldblum, & Leboyer, 1995), as well as early language deficits in siblings of children with ASD (Gamliel, Yirmiya, Jaffe, Manor, & Sigman, 2009), when compared with siblings of children with Down Syndrome and siblings of typically developing children, respectively.

In terms of social abnormalities and behavioural difficulties, impaired social conversational skills and non-social preferences were found in ASD parents, compared to parents of typically developing children (Landa et al., 1992), parents of children with Down Syndrome (Piven et al., 1997b), and parents of dyslexic and typically developing children (Briskman, Happe & Frith, 2001). Interestingly, impaired social responsiveness has also been revealed in siblings of children with Autistic Disorder relative to siblings of children with Pervasive Developmental Disorders (PDD) and siblings of children with other disorders, unrelated to autism, such as ADHD, affective disorder, or anxiety disorder (Constantino et al., 2006).

Other studies have demonstrated higher rates of specific personality traits, reflecting social deficits, such as aloofness, tactlessness, difficulty in being demonstrative and making friendships, intense preoccupations, rigidity, hypersensitivity to criticism, irritability, anxiousness, shyness, impulsivity, and eccentricity in relatives of children with autism, when compared with relatives of children with Down Syndrome (Murphy et al., 2000; Piven et al., 1997b; Piven et al., 1994; Smith et al., 2009). Besides findings indicating no more frequent mental health problems or cognitive deficits in relatives of individuals with autism (Szatmari et al., 1995), several research studies have also revealed increased rates of schizoid traits (Wolff, Narayan, & Moyes, 1988), schizoid depression (Bolte, Knecht, & Poustka, 2007), affective disorders, and particularly bipolar disorder, (DeLong & Dwyer, 1988), anxiety disorders (Piven et al., 1991), Obsessive-Compulsive Disorders (OCD) (Bolton et al., 1998), and alexithymia (lack of understanding of one's emotions and difficulties in verbalizing them) (Szatmari et al., 2008) in relatives of individuals diagnosed with ASD.

Apart from the behavioural phenotype research findings mentioned above, there

have also been several studies exploring the cognitive phenotype of autism. In their extensive review on previous research findings on the BAP in relatives of individuals with autism, Bailey et al. (1998) discussed several studies that showed no difference in ASD relatives' performance on tasks of central coherence, executive function and recognition of emotional facial expressions, when compared with controls (Fombonne, Bolton, Prior, Jordan, & Rutter, 1997; Ozonoff, Rogers, Farnham, & Pennington, 1993; Smalley & Asarnow, 1990; Szatmari et al., 1993). However, other studies have revealed significant cognitive functioning differences in parents of children with autism. In terms of executive function, ASD parents have been found to be impaired relative to parents of children with Down Syndrome (Piven & Palmer, 1997). In addition, in another study, parents and especially fathers of children with autism were shown to exhibit poorer attentional flexibility and planning skills in comparison to parents of learning disabled and typically developing children (Hughes, Leboyer, & Bouvard, 1997). More recently, in a study using oculomotor delayed-response tasks, Koczat, Rogers, Pennington, and Ross (2002) also reported spatial working memory deficits in ASD parents.

Other studies have also provided evidence for an enhanced cognitive processing style in relatives of individuals with ASD, supporting the enhanced non-social processing model (see *Chapter 1, Section 2*, of the literature review). Baron-Cohen and Hammer's (1997) findings revealed greater performance on central coherence tests in parents of children with Asperger's Syndrome (AS), when compared with controls, reflecting an *enhanced* local processing cognitive style in parents of the AS group (Baron-Cohen & Hammer, 1997). These findings were replicated by Happe, Briskman, and Frith (2001), who found that fathers of boys with autism performed better on central coherence tests relative to parents of boys with dyslexia and parents of typically

developing boys.

In terms of social cognitive development, several studies have also provided evidence for impaired processing of social cues, such as faces and eye-gaze, in parents and siblings of children with ASD. For example, parents and siblings of children with AS were found to be impaired in recognizing emotions and understanding mental states of faces, when they were shown only the eye region of the faces (Baron-Cohen & Hammer, 1997; Dorris et al., 2004). Greater deficits in emotion recognition were also found in parents and siblings of children with autism in families including more than one case of ASD, when compared with relatives of only one individual with ASD (Bolte & Poutska, 2003). Moreover, Scheeren and Stauder (2008) used a spatial attention task, on which ASD parents showed longer reaction times to social (eyes) than to non-social (arrows) cues, compared to control parents of typically developing children. Interestingly, Adolphs et al. (2008) investigated face processing and understanding of emotions in three groups of parents: a) ASD parents, b) ASD parents assessed as socially 'aloof' and c) parents of typically developing children. They showed that both ASD groups spent less time looking at the eye region, whilst the "aloof"' ASD group relied mostly on information provided by the mouth region. These findings provide evidence for a cognitive endophenotype in parents of individuals with autism, as they are consistent with the pattern of face processing found in children with ASD, which is characterized by reduced processing of the eye region and enhanced processing of the mouth region (Adolphs et al., 2008; Pellicano, 2008).

Notably, evidence for social cognition deficits in ASD relatives has also been provided by neuroimaging studies. Dawson et al. (2005) reported face recognition deficits in parents of children with autism, as well as an atypical brain response to faces

for the negative component N170. In addition, a pilot fMRI study by Baron-Cohen et al. (2006) revealed atypical brain activity in parents of children with AS during an emotion recognition and a visual search task. Similarly, Dalton and colleagues (2007) (Nacewicz, Alexander, & Davidson, 2007) used eye-tracking technology and found decreased eye gaze-fixation during a face recognition task, as well hypoactivation in the right fusiform gyrus and a reduced amygdala volume in siblings of children with autism. Finally, in an ERP study using auditory stimuli, both children with AS and their fathers were found to exhibit atypical cortical responses to affective speech prosodies (Korpilahti et al., 2007).

1.3.3. Behavioural evidence for a BAP from studies in high-risk infant and toddler siblings of individuals with ASD

Previous research revealing a risk of up to 20% for ASD in younger siblings of children diagnosed with ASD, as well as the need for early diagnosis and identification of prodromal early behavioural signs within the first 3 years of life, has led numerous research groups to examine several aspects of early development in infant and toddler ASD siblings, including motor functioning, receptive and expressive language development, joint attention, gesture use and imitation, social interaction behaviours (e.g. response to name, social smiling and social interest in others), and temperament characteristics (e.g. Landa & Garrett-Mayer, 2006; Toth, Dawson, Metzoff, Greenson, & Fein, 2007; Zwaigenbaum et al., 2005; see also, Bhat, Landa & Galloway, 2011; Rogers, 2009; Yirmiya & Charman, 2010).

In terms of motor development, postural impairments were found in a group of high-risk infants, who presented with decreased duration of posture bouts when

observed from 5 to 14 months of age (Iverson & Wozniak, 2007). Similarly, a more recent study by Nickel and colleagues (2013) (Nickel, Thatcher, Keller, Wozniak, & Iverson, 2013) revealed delays in the emergence of sitting, standing or even more advanced postures, as well as difficulties in changing postures in high-risk infant siblings relative to low-risk controls. In addition, studies examining motor stereotypies and repetitive behaviours revealed motor atypicalities in 12- and 18-month old infant siblings of children diagnosed with ASD (Loh et al., 2007; Ozonoff et al., 2008). More specifically, Ozonoff et al. (2008) found that 12-month old, high-risk infants, who were later diagnosed with ASD, displayed repetitive behaviours, such as rolling, spinning, and rotating objects, more frequently during an object exploration task than infants who were typically developing. Similarly, a study by Loh et al. (2007) revealed more frequent arm waving and "hands to ears" postures in the high-risk infant group, who later received an autism diagnosis (see also McCleery, Elliott, Sampanis, & Stefanidou, 2013, for a review, *Appendix C2*). However, Damiano et al. (2013) reported significant differences in rates of repetitive and stereotyped movements between high-risk and low-risk infant siblings at 15 months, even when high-risk infants later diagnosed with ASD were excluded from the analyses.

With regards to language development, previous studies have also revealed impairments in receptive and expressive language in both infant and toddler siblings of children diagnosed with ASD (e.g. Toth et al., 2007; Zwaigenbaum et al., 2005). In a study using the Mullen Scales of Early Learning (MSEL; Mullen, 1995), Landa and Carrett-Mayer (2006) found that high-risk toddlers, later diagnosed with an ASD, performed worse than typically developing toddlers on the motor and language MSEL scales at 14 months, and on all MSEL scales at 24 months. Interestingly, findings in a

group of high-risk toddlers, who did not develop autism, also revealed impairments in receptive language skills, as well as lower scores on the symbolic, social and total scales of the Communication and Symbolic Behavior Scales (Toth et al., 2007). A more recent study by Gamliel et al. (2009) found lower language ability scores in a subgroup of high-risk siblings relative to siblings of typically developing children at 14 to 54 months of age. The authors also reported that a subgroup (40%) of the high-risk group also exhibited cognitive and language deficits at 7 years of age, when compared to 16% of the low-risk controls (Gamliel et al., 2009). These findings were replicated by Hundry and colleagues (2013) who demonstrated that a reduced receptive vocabulary advantage distinguished high-risk from low-risk siblings at 14 months of age, which however was maintained only in high-risk siblings who developed ASD or other developmental delays by 24 months of age.

Along with previous research in language and motor development in infants and toddlers at risk for ASD, several research groups investigated nonverbal communicative behaviours, such as gestural communication and joint attention skills, as well as the coordination of motor and language skills (e.g.; Iverson & Wozniak, 2007; Toth et al., 2007; Yirmiya et al., 2006; Zwaigenbaum et al., 2005; see also, McCleery et al., 2013). Yirmiya et al. (2006) measured mother-infant synchrony during free play interactions and found a weaker mother-infant synchrony for infant-led interactions in 4-month old infant siblings of children diagnosed with autism, when compared with low-risk infants. In a follow-up at 14 months, they also reported that infants at risk for autism displayed fewer non-verbal requesting behaviours and performed worse than low-risk infants on the language scales of Bayley Scales of Infant Development (BSID; Bayley, 1993). In addition, Iverson and Wozniak (2007) found that high-risk infants experienced delays in

early communicative behaviours, such as reduplicated babble, showing and first word use, by 14 months, as well as language development delays at 18 months. Moreover, the authors examined the rate of rhythmic arm movements during pre-babble and babble onset sessions, which was found to be relatively unchanged across the sessions in high-risk infant siblings (Iverson & Wozniak, 2007; see also, McCleery et al., 2013).

Other social communicative behaviours that have been found to be impaired or atypical in high-risk infant and toddler siblings of individuals with ASD include joint attention and requesting behaviours (e.g. Bedford et al., 2012; Cassel et al., 2007; Cornew et al., 2012; Goldberg et al., 2005; Presmanes, Walden, Stone, & Yoder, 2007; Rozga et al., 2011; Sullivan et al., 2007; Yoder, Stone, Walden, & Malesa, 2009), response to name (e.g. Nadig et al., 2007; Zwaigenbaum et al., 2005), social smiling (Cassel et al., 2007; Toth et al., 2007; Zwaigenbaum et al., 2005), imitation skills (Zwaigenbaum et al., 2005), gestural communication (Mitchell et al., 2006; Toth et al., 2007), and face scanning focusing more on the mouth rather than the eye region (Merin, Young, Ozonoff, & Rogers, 2007). In addition, an early temperament characterised by passivity, atypical expression of distress, increased negative affect, decreased adaptability and atypical responses to other people's distress has also been documented by studies in infants and toddlers at risk for ASD (Clifford, Hudry, Elsabbagh, Charman, & Johnson, 2013; del Rosario, Gillespie-Lynch, Johnson, Sigman, & Hutman, 2013; Esposito, del Carmen Rostagno, Venuti, Haltigan, & Messinger, 2013; Hutman et al., 2010; Zwaigenbaum et al., 2005; see also Rogers, 2009; Yirmiya & Charman, 2010).

1.3.4 Social attention in infants and toddlers at risk for ASD

As mentioned in the previous section of this chapter, social attention has been found to be significantly impaired in individuals with ASD, relative to typically developing controls (e.g., Dawson et al., 1998; Klin et al., 2002a). This finding has been reported by both behavioural and neuroimaging research studies, also revealing a greater preference or enhanced processing of non-social cues in young ASD groups (e.g. Pierce et al., 2011; Webb et a., 2006). Social attention as reflected in social communicative behaviours, such as joint attention, response to name or social smiling, in infants' and toddlers' everyday social interactions with others, has also been examined in high-risk and low-risk infant groups by experimental studies using both social (e.g. faces, social scenes including an actor or speech sounds) and non-social stimuli (e.g. toys, non-speech analogues), in order to investigate social and non-social attention mechanisms in this high-risk population.

Despite findings revealing intact face orienting mechanisms and gaze behaviour in high-risk groups (Elsabbagh et al., 2013; Young, Merin, Rogers, & Ozonoff, 2009), several studies have also reported both impaired social attention, as well as enhanced non-social attention in high-risk groups (e.g. Chawarska, Macari & Shic, 2013; Noland et al., 2010). Chawarska, Macari and Shic (2013) employed an eye-tracking task, in which they presented a video containing both social (actress engaging in several different actions) and non-social cues (toys and table with food on it) to 6-month old high-risk and low-risk infants. The actress either spoke to the camera using infant-directed speech, or prepared some food looking down, or looked at the toys located in the four corners of the screen. The authors found that the high-risk group later diagnosed with ASD spent less time looking at the social scene relative to low-risk

controls (Chawarska, Macari & Shic, 2013). In addition, in accordance with previous findings in individuals with ASD (e.g. Klin et al., 2002a), infants at risk who developed autism attended less to the actress and her face when they looked at the social video, without exhibiting, however, non-social attentional preferences for the objects contained in the video (Chawarska, Macari & Shic, 2013). Interestingly, in another study of the same research group, infants were presented only with faces that were either neutral and still, or moving and smiley, or speaking a nursery rhyme (Shic, Macari & Chawarska, 2013). In general, high-risk infants who were later diagnosed with ASD attended less to the social scene presented (Shic, Macari & Chawarska, 2013). Additionally, they were found to spend less time looking at the inner parts of the faces when the person presented was speaking, suggesting that co-occurrence of speech may disturb social attention in high-risk siblings (Shic, Macari & Chawarska, 2013). These findings may be associated with previous findings revealing an impairment in audiovisual integration of speech cues in 9-month old infants at risk for ASD (Guiraud et al., 2012).

Along with the aforementioned findings of reduced attention to faces and social scenes in high-risk infant siblings who later developed ASD, other studies also demonstrated a tendency for enhanced non-social attention or preference in high-risk groups (e.g. Droucker, Curtin & Vouloumanos, 2013; Noland et al., 2010). For example, Droucker, Curtin, and Vouloumanos (2013) presented face visual displays or a checkerboard paired with infant- or adult-directed speech to infants at risk and low-risk controls at 6 to 18 months of age. Their findings revealed that both groups showed a preference for infant-directed speech relative to adult-directed speech, as well as for faces relative to checkerboards. However, the difference in looking times between facial stimuli and the checkerboard was greater for the low-risk group, as high-risk infants

spent significantly more time looking at the checkerboard than controls (Droucker, Curtin, & Vouloumanos, 2013). Similarly, Curtin and Vouloumanos (2013) examined speech (non-sense words) versus non-speech (non-speech analogues) preference in 12-month old infants with an older sibling with ASD, and demonstrated that, although there were no significant group differences, only low-risk infants showed a preference for speech relative to non-speech stimuli. In contrast, high-risk infants exhibited a tendency to spend more time listening to non-speech relative to speech sounds (Curtin & Vouloumanos, 2013). These findings of non-speech preference in the high-risk group are consistent with the aforementioned findings by Droucker and colleagues (2013), revealing a similar attentional imbalance between social and non-social cues and a preference for non-social stimuli in the visual domain.

This type of non-social preference has also been found by studies using live interaction experimental paradigms. In a recent study examining attention to social and non-social cues during a social-object learning task, Bhat, Galloway, and Landa (2010) showed infants a cause-and-effect toy on their righ-hand and trained them on the association of bending a joystick and the activation of the toy. The training period (acquisition) was followed by the extinction period, when the joystick stopped activating the toy. During all experimental conditions the caregiver was sitting on the infant's left and either remained silent (spontaneous phase) or initiated social interaction with the infant (social phase), using the same verbal prompts. The authors recorded infants' looking times to the caregiver and the toy, and found that high-risk infants attended less to the caregiver and more to the toy or the joystick during the spontaneous phase (Bhat, Galloway, & Landa, 2010). These findings are consistent with previous research evidence of impaired joint attention in infants and toddlers who are at risk of

developing ASD (e.g. Goldberg et al., 2005; Yoder et al., 2009), as well as with previous findings of an atypical non-social preference in high-risk groups (e.g. Droucker, Curtin, & Vouloumanos, 2013).

Interestingly, the latter was also revealed by a study of working memory in infant siblings of individuals diagnosed with ASD (Noland et al., 2010). Noland and colleagues (2010) employed a delayed-response task, including two experimental conditions (a social target and a non-social target condition), to measure reaction time in visual orienting and preferential looking in infant siblings of children with autism and low-risk infants at the age of 6.5 and 9 months. They found that high-risk infant siblings performed better, exhibiting higher working memory accuracy, than low-risk infants in the non-social target experimental condition by 9 months of age. The researchers interpreted their finding as a "non-social working memory advantage" in high-risk infant siblings (Noland et al., 2010).

Findings of atypical non-social attention in infants at risk for autism are extended by studies of visual attention and object exploration. More specifically, infants at risk for ASD have been found to exhibit “sticky attention” patterns by 12 months of age, which are mainly characterised by difficulties in disengaging their attention from non-social cues to attend to different targets and have been suggested to be associated with diagnostic outcomes of ASD at a later age (Elsabbagh et al., 2013; Elsabbagh et al., 2009b; Sacrey, Bryson & Zwaigenbaum, 2013; Zwaigenbaum et al., 2005). In fact, this type of “sticky attention” to non-social targets (e.g. objects) has also been reported by parents of infants at risk (Zwaigenbaum et al., 2005), and has also been observed by studies investigating object exploration while infants engage in play activities (Koterba, Leezenbaum & Iverson, 2012). By 9 months of age, high-risk infants have been found

to spend more time looking at toys available in a room than low-risk controls (Koterba, Leezenbaum & Iverson, 2012). In addition, as previously mentioned, Ozonoff et al. (2008) reported repetitive behaviours and atypical visual exploration and use of toys in 12-month old high-risk infants who later developed ASD. However, it is still unknown whether this tendency for atypical non-social attention in high-risk groups is associated with reduced motivation to attend to social cues in the environment and the development of non-social interests, or with difficulties in spatial orienting and visual disengagement (see also, Koterba, Leezenbaum & Iverson, 2012; Ozonoff et al., 2008).

1.3.5 Social processing in infants at risk for ASD – Evidence from neuroimaging research

Recent neuroimaging research in infants at risk for autism has contributed to the identification of early ASD biomarkers and a shared neuroendophenotype in children with ASD and their younger siblings by revealing brain structural and functional atypicalities in high-risk groups (e.g. Keehn, Wagner, Tager-Flusberg, & Nelson, 2013; Shen et al., 2013). Previous studies in high-risk infants have shown atypical intra- and inter-hemispheric functional connectivity over the first year (Keehn et al., 2013), larger cerebral volumes over the first and second years (Shen et al., 2013), and differences in multiscale entropy as a resting state EEG measure over the entire scalp and especially the frontal cortex (Bosl et al., 2011). In addition, recent studies in infants at risk for ASD have also revealed atypical development of white matter at 6 and 7 months (Elison et al., 2013; Wolff et al., 2012), which has also been associated with visual orienting deficits in infants later diagnosed with ASD (Elison et al., 2013).

As communication and social impairments constitute the core deficits in ASD, social processing, and especially face and eye-gaze processing, has been the focus of most recent electrophysiological and neuroimaging studies in high-risk infant and toddler siblings of children with ASD. In an ERP study presenting familiar (mother) and unfamiliar (stranger) faces to 12-month old high- and low-risk infants, Luyster et al. (2011) found almost no group differences apart from a larger peak amplitude for a late perceptual processing response to faces (P400) in infants at risk. Similarly, Key and Stone (2012a) employed an oddball ERP paradigm and eye-tracking methodology, in order to investigate how 9-month old high-risk infants and low-risk controls process familiar (mother) versus unfamiliar faces (stranger). Eye-tracking recordings revealed similar scanning patterns in both groups, and ERPs showed no group differences, apart from a significant difference in the latency of a late perceptual processing response (P400) to the stranger face, which was delayed only in the low-risk group (Key & Stone, 2012a). In addition, in another ERP study, the same authors employed an oddball ERP paradigm containing standard unfamiliar faces and deviant faces with different facial features (eyes or mouth) (Key & Stone, 2012b). Their results revealed that both high- and low-risk groups exhibited differential ERP responses to changes in facial features, although they used different brain mechanisms (Key & Stone, 2012b). More specifically, only the low-risk group exhibited faster face processing (N290) responses to the deviant relative to the standard facial stimuli, while their N290 latencies to facial feature changes were also shorter than those of the high-risk group (Key & Stone, 2012b). Moreover, a more recent fNIRS study in 7-month old infants reported greater deoxy-hemoglobin responses to the mother's face in high-risk infants (Fox, Wagner, Shrock, Tager-Flusberg, & Nelson, 2013). However, the high-risk group did not exhibit

differential responses to the mother's neutral face relative to her smiley face, in contrast to the low-risk group (Fox et al., 2013). Finally, Elsabbagh et al. (2009a) used images of faces with direct or averted gaze and demonstrated that 10-month old ASD infant siblings showed a prolonged P400 ERP response to direct gaze over the occipital cortex relative to control infants. Interestingly, infant ERP responses to eye-gaze shifts have been associated with a later ASD diagnosis, whereas larger P400 responses to direct gaze have been associated with less restricted interests and repetitive behaviours at 3 years of age (Elsabbagh et al., 2012).

In parallel with electrophysiological and neuroimaging studies examining the neural processing of social stimuli in the visual domain, a few recent studies have also investigated how infants at risk for ASD process auditory social stimuli, such as speech and non-speech adult vocalizations (see also next section) (Lloyd-Fox et al., 2013; Seery, Vogel-Farley, Tager-Flusberg, & Nelson, 2012). For example, a recent ERP study used an oddball paradigm including standard native speech sounds, deviant native speech sounds and deviant non-native speech sounds (Seery et al., 2012). Although ERP responses were similar in both high-risk and low-risk groups, lateralization to speech was absent for a negative late slow wave (300-700ms) over the central cortex in infants at risk for ASD, in contrast to controls (Seery et al., 2012).

1.3.6 Social versus non-social processing in infants at risk for ASD – Evidence from electrophysiological studies

Along with atypical processing of social cues, a few recent EEG/ERP studies have also extended previous behavioural research findings by revealing enhanced non-social processing in infants at risk for ASD. In a study of visual sensory processing in

6-month-old infant siblings of children with autism, McCleery, Allman, Carver, and Dobkins (2007) used a forced-choice preferential looking paradigm to test whether the subcortical system associated with face processing, and especially the magnocellular pathway, develops normally in infants at-risk for autism. The infants were shown a screen with a centrally located rotating stimulus, which preceded the onset of non-social, chromatic (parvocellular pathway stimulus) or luminance (magnocellular pathway stimulus) simple gratings on the left or right. Interestingly, the results showed that high-risk infants exhibited atypical enhanced processing of the magnocellular, but not the parvocellular pathway stimulus. These findings indicate that 6-month-old infant siblings of children with autism probably exhibit enhanced luminance-contrast sensitivity compared with infants with no family history of autism and highlight the *enhanced* instead of the *impaired* character of non-social, visual sensory processing in high-risk infants (McCleery et al., 2007).

In a more recent study, McCleery, Akshoomoff, Dobkins, and Carver (2009) presented pictures of faces and objects (toys) to 10-month-old high-risk and low-risk siblings and used ERPs in order to measure cortical responses to faces and objects. Their findings replicated previous research findings of atypicalities in face and object processing in children and adults with autism, revealing atypical cortical responses for the latencies of N290 and P400, as well as a lack of hemisphere asymmetries in high-risk infants. Importantly, though, the high-risk group exhibited faster cortical responses to pictures of objects relative to low-risk controls, providing additional evidence for potential enhanced non-social processing in high-risk infants (McCleery et al, 2009).

In addition, Lloyd-Fox et al. (2013) conducted an fNIRS study in order to investigate how 4- to 6-month old infants at risk for ASD process non-speech adult

vocalizations (e.g. crying sound) versus environmental sounds (toy sound). Their results showed that high-risk infants did not exhibit significant haemodynamic responses to non-speech vocalizations over the temporal cortex, as opposed to the low-risk group. However, there was a trend for the neural responses to the environmental sounds to be more robust in the high-risk group (Lloyd-Fox et al., 2013).

The aforementioned findings extend previous behavioural and neuroimaging research revealing a trend for enhanced non-social attention or preference for non-social stimuli, such as objects, audiovisual synchronies and non-speech sounds in both individuals with autism (e.g. Klin et al., 2002a; Kuhl et al., 2005; Pierce et al., 2011; Shultz, Klin, & Jones, 2011) and their younger siblings (e.g. Chawarska, Macari & Shic, 2013; Curtin & Vouloumanos, 203; Droucker, Curtin & Vouloumanos, 2013; Noland et al., 2010). In addition, findings by McCleery and colleagues (2009) in high-risk infants replicated previous ERP findings of enhanced neural responses to objects relative to faces in children with ASD (Webb et al., 2006).

1.4 Conclusions

In sum, the first section of the literature review presented in the current chapter outlines previous behavioural and neuroimaging research in human action and biological motion processing, as well as human voice and speech processing, in typically developing infants, children and adults. The results revealed from these studies in typical development reflect the established typical developmental trajectory of visual human motion and action processing. Notably, they also provide evidence for shared brain mechanisms associated with both visual and auditory processing of social stimuli,

such as human actions and voice. In addition, the second section of the current literature review presents previous studies exploring social attention and social processing mechanisms in children and adults on the autism spectrum, with a focus on visual processing of biological motion and human actions. Finally, the last section summarises the previous literature and research in social attention and perceptual processing mechanisms in infant and toddler siblings of individuals with ASD, who may share a similar endophenotype with their siblings and may therefore be at higher risk of developing autism.

Based on previous research studies and findings discussed in the current literature review, there is a gap in the literature with regards to social processing mechanisms in the auditory modality both in typical and atypical development in infancy and early childhood. More specifically, although there have been numerous research studies exploring the visual perceptual processing of other people's actions in typically developing infants and children, very little is known about auditory social processing in toddlers and young children. Based on previous findings in adults revealing the existence of specialist brain mechanisms associated with the perceptual processing of auditory human actions, the investigation of similar mechanisms in children may help to establish the early typical developmental trajectory of both visual and auditory neural mechanisms underlying social development. Most importantly, the examination of the development of these mechanisms in children with social and communication disorders, such as children with ASD and toddlers who are at risk of developing autism, may further our understanding of the disorder and the nature of ASD-related behavioural symptoms and social communication difficulties. In addition, it may contribute to the

development of early diagnostic methods (through the use of electrophysiological measures) and more effective behavioural intervention programmes.

In the following chapters, we present the methodology employed in the present studies, as well as discuss the results revealed in our studies examining auditory social processing mechanisms both in typically developing toddlers and children, and young children with autism and their toddler siblings.

CHAPTER 2:

METHOD

2.1 Electroencephalography (EEG) and Event-Related Potentials (ERPs)

Early human development has been broadly studied by numerous developmental and cognitive psychology research groups investigating different aspects of language, social and cognitive development, such as joint attention, pretend play, Theory of Mind, executive function and imitation. However, the main goal of developmental neuroscientists over the last two decades has been the investigation of the relation between brain activity and cognitive, emotional and social development in infancy and early childhood through the use of neuroscientific measures, such as functional magnetic resonance imaging (fMRI), Electroencephalography (EEG) and Event-related Potentials (ERPs) (de Haan, 2007; Nelson & Luciana, 2001; Nelson & McCleery, 2008;).

Unlike fMRI, EEG and ERPs are more practical for use in infants and children younger than 6 years of age, as well as in children with developmental delays or neurodevelopmental disorders, due to limitations in language or motor development (de Haan, 2007; Nelson & McCleery, 2008). EEG was first used by Hans Berger (1929) and is a noninvasive technique that allows researchers to record and measure the natural electrical activity produced by the human brain from electrodes placed on the scalp (de Haan, 2007; Luck, 2005; Nelson & McCleery, 2008). Although, both EEG and ERPs are used to record brain activity, they reflect different aspects of brain functioning (de Haan, 2007). EEG represents the ongoing electrical activity in the brain and is usually used to measure different rhythms when the brain is at a resting state, coherence between regions or event-related synchronisation (de Haan, 2007). On the other hand, ERPs reflect changes in the brain's electrical activity volume in response to different stimuli or events (de Haan, 2007; Nelson & McCleery, 2008). This activity volume is

produced by the synchronous activation of electrical fields associated with neuronal activity in the brain (Nelson & McCleery, 2008). In addition, ERPs provide high temporal resolution of at least 1ms, which can be highly informative, especially in studies of atypical development (Luck, 2005; see also Nelson & McCleery, 2008). Most importantly, latest advances in ERP research has allowed researchers to use higher-density arrays of electrodes, which allow for greater spatial sampling and the identification and distinction of more positive or negative deflections (so-called components) based on scalp topography (Nelson & McCleery, 2008; see also Johnson et al., 2001). Numerous previous ERP studies examining the neural correlates for sensory processing or mismatch negativity (MMN), face processing, speech and language processing, or cognitive processes, such as executive functioning, memory and attention, in infants and young children, have significantly contributed to the better understanding of both typical and atypical development (Nelson & Luciana, 2001; Nelson & McCleery, 2008).

2.2 Repetition Suppression (RS)

Repetition Suppression (RS) has been studied in previous fMRI, EEG/ERP, as well as Magnetoencephalography (MEG) studies, in order to measure neural processing efficiency or to explore the nature of representations in different brain regions (Grill-Spector, Henson & Martin, 2006). It is an experience-related neural process, used to describe the reduction of neural activity in response to repeated stimuli, as a consequence of "predictive coding" and neural adaptation to the perceptual properties of the stimuli (Grill-Spector, Henson & Martin, 2006). More specifically, when a stimulus is repeated or followed by a similar stimulus from the same perceptual category, the

mean firing rate of neurons that responded to the initial stimulus decreases due to short-term habituation (Henson & Rugg, 2003). In contrast, when a stimulus is followed by a stimulus from a different perceptual category neural mechanisms are released as a result of a prediction error caused (Baldeweg, 2006). Several different models have been described to explain repetition suppression: a) the "fatigue" model, which describes repetition suppression as a firing-rate adaptation mechanism or alternatively as the result of "reduced synaptic efficacy of specific synapses from connected neurons", b) the "sharpening" model which predicts that populations of neurons that process features of the stimuli that are not necessary for their identification are suppressed when the stimuli are repeated, resulting in the reduction of the number of neurons firing, and c) the "facilitation" model, which explains repetition suppression as a result of faster neural processing or shorter latencies of neural activity (Grill-Spector, Henson & Martin, 2006).

Previous studies using RS paradigms have utilised both visual (e.g. faces) and auditory (e.g. tones, action or speech sounds) stimuli in order to explore the neural mechanisms underlying the perceptual processing of social and non-social stimuli further (e.g. Baldeweg, 2006; Giusti et al. 2010; Pizzamiglio et al., 2005; Summerfield, Trittschuh, Monti, Mesulam, & Egner, 2008). In the present studies, a novel auditory-auditory, repetition suppression ERP paradigm was utilised for the investigation of perceptual processing of sounds produced by human actions and object or environmental sounds in typically developing young children, toddlers and young children with ASD and toddlers at risk for ASD.

2.3 Development of Auditory-Auditory Repetition Suppression Event-Related Potentials (ERP) Paradigm

2.3.1 Stimuli

Two types of auditory stimuli were selected for the development of the auditory-auditory repetition suppression ERP paradigm that was utilised in the present studies; these included two types of sounds produced by human and non-human actions. Human action sounds were produced by a simple hand action (hands clapping) and a hand action involving an object (hands ripping a paper), whereas non-human action sounds included an object sound (sound produced by helicopter blades spinning) and an environmental sound (ocean waves sound). The selection of both a simple hand action and a hand action involving an object for this ERP paradigm was based on the RS ERP paradigm employed by Giusti et al. (2010), who showed that both types of action stimuli activated a distinct neural network associated with action-related sound processing in adults. Notably, recent EEG findings in infants have also revealed that specialist neural mechanisms associated with the perceptual processing of human action sounds associated with objects start to develop by 8 months of age (Paulus et al., 2012) (see also *Chapter 1*).

All auditory stimuli used in the present studies were extracted from short digital video clips of the actions mentioned above. There were 4 different digital video clips for each human and non-human action sound type (e.g., 4 different exemplars of the hand clapping action producing a different clapping sound) (see also Giusti et al., 2010). The sound stimuli were presented as .wav files (16-bit, 44.1 kHz sampling), and stimulus duration ranged from 790 to 1250 ms with a mean duration of 1020ms in order to achieve category-specific effects (see also Kuehl et al., 2013; Nemrodov & Itier, 2012)

(see *Table 1*). A paired sample t-test revealed no significant differences between the duration of human (*M*=917ms, *S.E.*=37) and non-human action sounds (*M*=989ms, *S.E.*=47.6), ($t(7)=-1.33$, $p> 0.05$). Average intensity of human and non-human action sounds was equalised to be 65 dB.

The auditory stimuli utilised in the present ERP paradigm were carefully selected, considering participants' previous experience with the actions producing them. More specifically, young children are usually familiar with the clapping and ripping actions used here, as well as the sounds produced by them, by 24 months of age (e.g. Sheridan, 1997). In fact, infants are usually able to coordinate hand movements and perform actions, such as banging bricks together or ripping paper, as well as clapping hands and playing "pat-a-cake" by 12 months of age (e.g. Sheridan, 1997). In addition, water sound and sounds produced by car engines, aeroplanes or helicopters are usually highly familiar and interesting to young toddlers, as actions involving these sounds (e.g., pouring water) and toys associated with them (e.g., aeroplane) have been found to be included in the subjects of intense interest in young children (DeLoache, Simcock, & Macari, 2007). In addition, these subjects of interest have been found to be well developed by 24 months of age (DeLoache, Simcock, & Macari, 2007).

Human Action Sounds		Non-Human Action Sounds	
Hand Clapping Sound		**Helicopter Blade Spinning Sound**	
Exemplar 1	967 ms	*Exemplar 1*	800 ms
Exemplar 2	787 ms	*Exemplar 2*	1,081 ms
Exemplar 3	786 ms	*Exemplar 3*	941 ms
Exemplar 4	800 ms	*Exemplar 4*	882 ms
Ripping Paper Sound		**Ocean Wave Sound**	
Exemplar 1	1,000 ms	*Exemplar 1*	964 ms
Exemplar 2	997 ms	*Exemplar 2*	998 ms
Exemplar 3	997 ms	*Exemplar 3*	1,250 ms
Exemplar 4	999 ms	*Exemplar 4*	999 ms

Table 1. *Duration of auditory human and non-human action stimuli in milliseconds (ms).*

2.3.2 Auditory-Auditory Repetition Suppression ERP Paradigm

The auditory-auditory repetition suppression ERP paradigm was implemented using E-Prime (Schneider, Eschman, & Zuccolotto, 2002) and included a single block of approximately 570 trials (see also Giusti et al., 2010). Four trial types were included in the paradigm, which were presented in randomised order, with a probability of 25% each. These four trial types included: a) the congruent (or repetition) human action sound trial which involved the repetition of human action sounds (e.g. hands clapping sound→hands clapping sound, or paper ripping sound→paper ripping sound), b) the incongruent (or non-repetition) human action sound trial which involved the non-repetition of human action sounds (e.g. helicopter blades spinning sound→hands

clapping sound, or ocean wave sound→paper ripping sound), c) the congruent (or repetition) non-human action sound trial which involved the repetition of non-human action sounds (e.g. helicopter blades spinning sound→helicopter blades spinning sound, or ocean wave sound→ocean wave sound), and d) the incongruent (or non-repetition) non-human action sound trial which involved the non-repetition of non-human action sounds (e.g. hands clapping sound→helicopter blades spinning sound, or paper ripping sound→ocean wave sound) (see *Figure 1*). Note that the trial type is defined here in relation to the second stimulus in the trial, and specifically whether or not that second stimulus is a repetition or non-repetition of the sound that preceded it. In each trial type, the first stimulus was defined as the "prime" stimulus and the second stimulus as the "target" stimulus, with the processing of the "target" stimulus expected to be affected by repetition suppression (see also Giusti et al., 2010; Pizzamiglio et al., 2005). In the congruent trials, although the first and second stimuli were from the same perceptual category, they were different exemplars of the same auditory stimulus (e.g. clapping sound 1→clapping sound 2). In the incongruent trials, the clapping sound exemplars were paired with the helicopter blade spinning sounds and the paper ripping sound exemplars with the ocean wave sounds. The reason why the auditory stimuli were paired in this way is because the clapping and the helicopter blade spinning sound exemplars were slightly sharper, whereas the paper ripping and the ocean wave sounds were smoother.

The inter-stimulus interval between the first and second auditory stimuli within each trial was 150 ms (see also Kuehl et al., 2013; Pizzamiglio et al., 2005), and the inter-trial interval varied between 900 ms and 1200 ms (see *Figure 1*). Epochs were time-locked to the second auditory stimulus in the trial, contained 100 ms pre-stimulus

time and 700 ms post-stimulus time (e.g. Lepisto et al., 2006; see also Luck, 2005), and were organised by stimulus type. The differences in brain activity elicited by repeated (suppressed neural mechanisms) and non-repeated (released neural mechanisms) stimuli were examined and compared separately for human and non-human action sound processing.

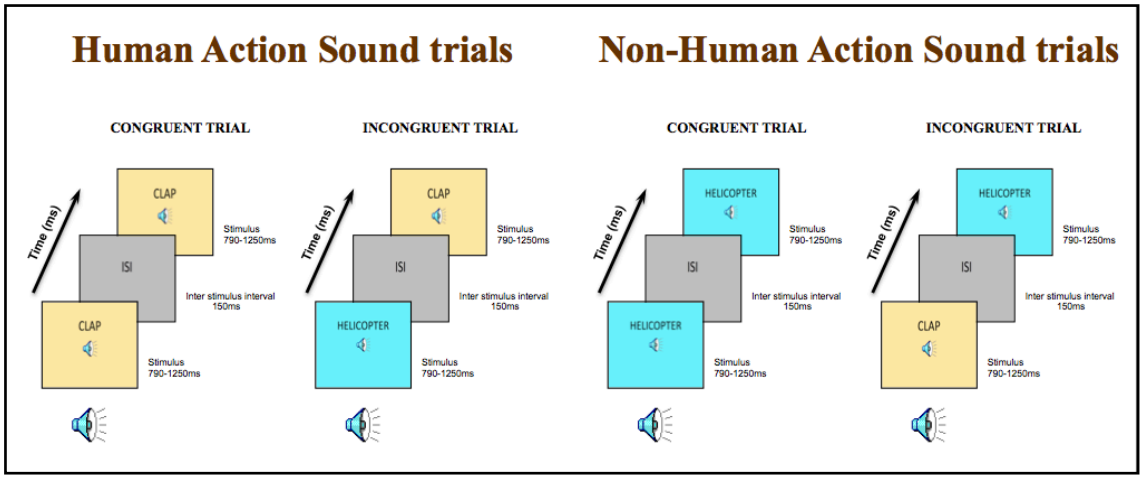

Figure 1. *Auditory-auditory repetition suppression ERP paradigm.*

Four different trial types were presented, each of which involved only auditory stimulus presentation. In RS paradigms, Condition (Human, Non-Human) is defined by the second stimulus in the trial, and Trial Type (Repetition, Non-Repetition) is defined by the first stimulus in the trial, separately for Human and Non-Human action sound trials.

2.3.3 Experimental Procedure

Participants sat in a sound-attenuated EEG/ERP testing chamber, either on their own next to an adult experimenter and/or their parent, or on their parent's lap. Parents were instructed to avoid any interaction with their child during the ERP assessment and to model sitting quietly and watching the video. Before the auditory EEG/ERP recording, all participants were shown four different exemplars of short audiovisual digital video clips of each of the human and non-human action sound stimuli used in the experiment, two times each, in order to be familiarised with them. During the actual

auditory-auditory repetition suppression ERP recording, participants listened passively to the sounds associated with the same human and non-human actions that were initially presented in the audiovisual digital video clips, but without the accompanying visual clips. Instead, during the actual auditory-auditory repetition suppression ERP experiment, participants were shown a silent cartoon video of their choice (e.g. Thomas the Tank Engine, Peppa Pig) while the human and non-human environmental and object sound stimuli were played via audio speakers (see *Figure 2*) (see also Kuhl et al., 2005; Whitehouse & Bishop, 2008). All participants were shown the same list of six cartoon videos to choose from. Some of the cartoon videos that were used to entertain participants during the ERP assessment contained fragments of human actions. However, none of the videos included any of the categories of stimuli used in the ERP paradigm (e.g. figures clapping hands or ripping paper, helicopters or aeroplanes, or any water related visual stimuli that could be associated with the ocean wave sounds). If children became fussy or bored, they were also allowed to hold their favourite puppets, or sensory toys of their preference during the assessment. All participants sat approximately 60 cm from the audio speakers. The EEG/ERP testing session lasted for approximately 30 minutes.

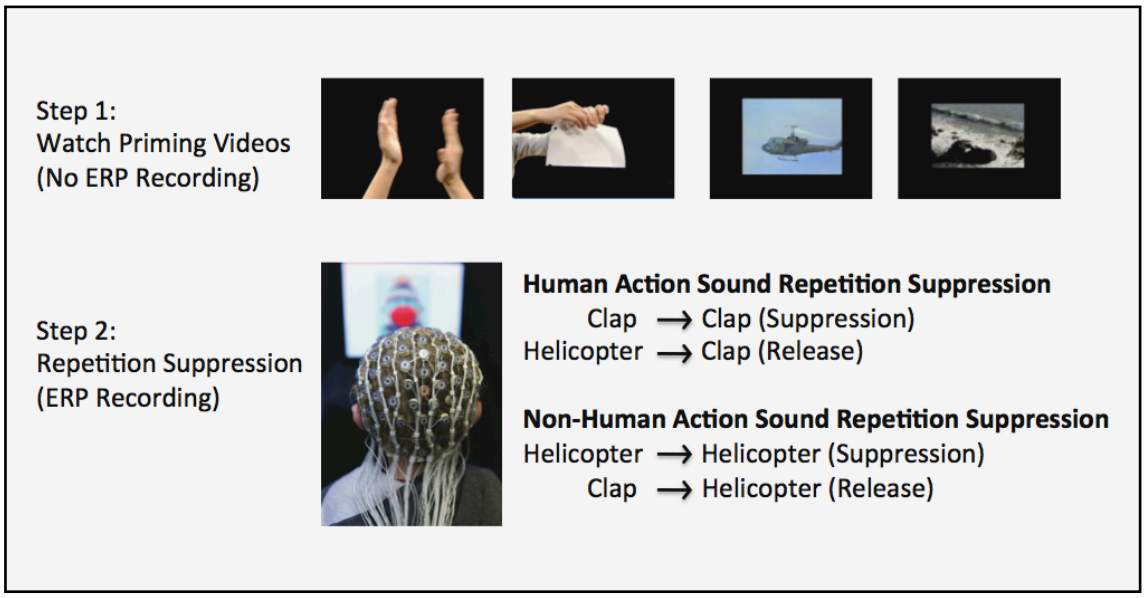

Figure 2. *Overall research design.*

Prior to EEG sensor net application, all participants were presented with 16 short auditory-visual clips (4 videos of each human or non-human action stimulus), each of which presented the auditory stimuli used in the RS ERP experiment, with accompanying visual actions. Following this, the EEG sensor net was applied to the participant's head, and the RS ERP experiment was initiated. During this actual ERP experiment, the participants were presented with the auditory portion of the stimuli only, while they watched an unrelated video of their choice.

2.3.4 ERP Recording

Brain electrical activity was recorded continuously using a child-friendly, high-density, 128-channel HydroCel Geodesic Sensor Net (HCGSN, Electrical Geodesics Inc., Eugene, Oregon) (Tucker, 1993). EEG was referenced to a single vertex electrode, Cz (sample rate = 500 Hz). All bioelectrical signals were recorded using Electrical Geodesics Inc. (EGI) amplifiers with an input impedance of less than 100 kΩ.

2.4 Ethical Considerations

2.4.1 Sources of Materials

Brainwave and behavioural data were collected from 2- to 6-year old typically developing toddlers and young children, 4- to 6-year old children diagnosed with ASD, and 2- to 3-year old toddlers at risk of developing autism, or presenting with ASD behavioural traits. All consent forms, which included the child's name, were kept in a locked area of the Infant and Child Laboratory at the School of Psychology, University of Birmingham, to which only the investigators and research assistants working directly on the project had access. Participants were identified by an identification number for coding purposes. The same codes were used to identify participants' brain activity data.

All research assistants and undergraduate students who worked on this project reviewed forms that describe the Society for Research in Child Development's Ethical Standards for Research with Children, as well as the specific subject confidentiality procedures for this particular research project as outlined in the approved ethics protocol.

No identification of individual subjects has been or will be used in any publications or presentations related to this study. Information regarding the identity of the participants will be kept until the results of the study are published. A list of participants has been maintained for the purpose of informing parents of the overall results of the study. However, the specific identity of subjects and the coded identification numbers will not be kept after publication.

2.4.2 Protection against Risks

Potential risks were minimized by maintaining good lab sanitation, clear and informative communications with parents, by providing clear guidance in confidentiality procedures for all research assistants, and by ensuring that access to personally identifying information was provided on a very limited basis.

There are no known risks associated with the brainwave recordings. The salt-water solution used for the electrode net cleaning before each testing session is not toxic or dangerous. In addition, a damp cloth was used to wipe the child's face, if water dripped on their face or eyes during the testing, as well as to wipe their face and head at the end of the testing session.

Despite the above-described precautions, some children might not like having the sensor net placed on their heads, or having strangers touch their heads. For this reason, the researcher first used a variety of other hats that children could play with and wear in the playroom prior to the ERP assessment. As soon as children became familiar with the researcher, they were shown the Sensor Net in a child-friendly way (e.g. the Sensor net was presented as a swimming hat with sponges or Fireman Sam's funny hat, depending on child's interests) and were allowed to touch it. During the electrode net application, videos and music toys were also presented to the children to make the procedure more pleasant for them and minimize the chances that they would become upset. Visual strategies and positive verbal or small tangible rewards were also used for some children in order to reduce their anxiety levels and make them feel comfortable. Parents were also allowed to be with their children at all times during the ERP assessments. Testing was interrupted if either the child or the parent became uncomfortable and they were given the opportunity to have a break or come back another day to complete the

assessment; otherwise, their participation in the study was discontinued without penalty. If children became upset during electrode net application, testing was discontinued.

2.4.3 Potential Benefits of the Proposed Research to the Subjects and Others

There were no direct benefits to individuals who participated in this research, or to others. The parents were clearly informed that the researchers were not trained to make clinical interpretations of EEG/ERPs, as clinicians do, and would not be able to provide them with any information about any implications of the test for their child's health. Instead, it was clarified that this research would further our understanding of the developmental trajectory of gesture and action perceptual processing in young children, which may be very important for the development of social and communication skills in early childhood. In addition, it was highlighted that the present research studies aimed to further our understanding of brain mechanisms underlying the core symptoms of Autism Spectrum Disorders, such as communication and social interaction deficits, and that the results of the study may eventually contribute to the development of more effective assessment and intervention strategies, based on the knowledge gained from electrophysiological measures.

CHAPTER 3:

HUMAN AND NON-HUMAN ACTION SOUND PROCESSING IN TYPICALLY DEVELOPING TODDLERS AND YOUNG CHILDREN

Abstract

Background: Extensive research has revealed the existence of specialist neural mechanisms associated with the visual and auditory perceptual processing of other people's actions in infants and adults. However, it is still unknown when these mechanisms start to develop and whether they exist in toddlers and young children. The aim of the current study was to investigate the time course and neurodevelopmental trajectory of perceptual processing of human action versus non-human action sounds in toddlers and young children. **Method:** A novel auditory-auditory, repetition suppression, event-related potentials (ERPs) paradigm was utilised, in order to investigate the nature and time-course of the neural mechanisms associated with the perceptual processing of sounds produced by human action sounds versus object or environmental sounds in 2-year old toddlers and 4- to 5-year old children. **Results:** Results in both age groups revealed early sensory deflections over the frontal and temporo-parietal sites, associated with both human- and non-human-action sound processing. N4 and P3 components also peaked at a later stage of cognitive processing only in response to action-related sounds, in both age groups. However, the N4 component was found to be right lateralized in the toddler group, whereas older children did not exhibit any such lateralization effects. **Conclusion:** Together, these findings further our understanding of the neurodevelopmental trajectory of human and non-human action-related sound processing in toddlers and young children. In addition, they contribute to a growing body of evidence for the existence of specialist neural mechanisms for the perceptual processing of human actions and gestures early in development, which may also contribute to social and communication development in early childhood.

3.1 Introduction

The detection and perception of sensory, motor, and affective aspects of other people's actions, including human movements, gestures, actions on objects, or even vocalizations, is critical for the understanding of their intentions or affective states as well as the development of effective social interaction, and has been suggested to begin developing at an early age in human life (e.g. Bertenthal, 1993; Blake & Shiffrar, 2007). In fact, previous studies have demonstrated that even newborn infants prefer to attend to visual or auditory stimuli related to human movement or vocalizations, over other forms of visual or auditory, non-human motion, such as randomly moving drifting dots or synthetic sounds (e.g. Simion et al., 2008; Vouloumanos et al., 2010). Other behavioural research findings have further revealed the ability of infants to discriminate canonical biological motion from scrambled motion (Bertenthal et al., 1987; Reid et al., 2005), as well as a preference for upright over inverted Point-Light Displays (PLDs), depicting biological motion in animated figures, in both infants (Fox and McDaniel, 1982; Simion et al., 2008) and toddlers (Klin et al., 2009).

Previous observations of this early capacity in infants has given rise to the investigation of the "social brain" and the neural mechanisms underlying the detection and perception of visual stimuli of biological motion or human actions in infants and children (Grossman and Johnson, 2007; see also Brothers, 1990; Carter & Pelphrey, 2006). The "social brain" is thought to include a large network of neuroanatomical structures that have been associated with social perception, such as the superior temporal sulcus (STS) and the frontal cortical regions, which have been found to be involved in biological motion and action processing (Carter & Pelphrey, 2006).

Recent event-related potentials (ERPs) studies investigated biological motion processing in infancy and revealed differences in the way infants process canonical versus scrambled or biomechanically impossible motion (Hirai and Hiraki, 2005; Marshall & Shipley, 2009; Reid et al., 2008), as well as upright versus inverted PLDs (Reid, Hoehl, & Striano, 2006). More specifically, both canonical versus scrambled motion and upright versus inverted PLDs were found to elicit larger, right lateralized, positive activity within the latency range of 200 to 300ms over parietal (Reid, Hoehl, & Striano, 2006) and occipito-temporal electrode sites (Hirai and Hiraki, 2005) in 8-month old infants. These findings are consistent with the findings of a recent functional near-infrared spectroscopy (fNIRS) study in 7- to 8-month old infants, which revealed right hemisphere activation, elicited by upright PLDs depicting facial movement, as opposed to static figures or inverted PLDs (Ichikawa et al., 2010). On the other hand, scrambled or biomechanically impossible motion was found to elicit a later, positive bilateral activity within the latency range of 300 to 700ms over mid-parietal channels in 8-month old infants (Hirai and Hiraki, 2005; Reid et al., 2008), and a greater, but slow, positivity within the latency range 500-600ms over lateral parietal and temporal sites in 5-month old infants (Marshall & Shipley, 2009).

In addition, electroencephalography (EEG) power studies have provided evidence for greater neural activity over frontal, central, and temporo-parietal electrode sites during human visual action observation in 8-month old infants (Reid, Belsky, & Johnson, 2005), 14-month old infants (Marshall et al., 2011; van Elk et al., 2008), and 18- to 30-month old toddlers (Warreyn et al., 2013). In accordance with previous findings in adults (e.g. Iacoboni et al., 1999; Rizolatti, Fogassi, & Gallese, 2001), an EEG study by Lepage and Theoret (2006) in four- to eleven-year old children revealed

mu rhythm suppression during both action observation and action execution. Other studies employing fNIRS in 5-month old infants and functional Magnetic Resonance Imaging (fMRI) in school-age children have identified a neural network of frontal, parietal, and temporal sites, involved in biological motion and human movement processing, including eye-gaze, mouth movements, and hand actions (e.g. Carter & Pelphrey, 2006; Lloyd-Fox et al., 2011; Lloyd-Fox et al., 2009; Mosconi et al., 2005). Notably, Lloyd-Fox et al. (2011) reported a shift for a greater activation of the right cortex in this region in response to human movement, in 5-month old infants. Together, these findings provide convincing converging evidence for specialist mechanisms underlying visual biological motion processing mechanisms in infancy and early childhood.

Although a number of neuroimaging studies have examined the visual processing of human actions in infancy, very little developmental neuroimaging research has focused on the auditory processing of human actions. At the same time, however, behavioural evidence suggests that sounds associated with human actions may also elicit the activation of specialised neural processing mechanisms (e.g. Vouloumanos et al., 2010). Furthermore, evidence from research on monkeys has revealed the existence of auditory and auditory-visual mirror neurons, which discharge during both action execution and passive listening to action-related sounds (Kohler et al., 2002). Follow-up studies using neuroimaging in human adults suggest that there are areas in the human brain with similar auditory and auditory-visual mirroring properties, including an auditory attentional network of bilateral frontal and parietal areas, as well as the posterior superior temporal sulcus (STS) (Bidet-Caulet et al., 2005; Kaplan & Iacoboni, 2007; see also, Aglioti & Pazzaglia, 2010).

Along with previous neuroimaging research, recent EEG/ERP studies employing mismatch negativity (MMN) and repetition suppression (RS) experimental paradigms have revealed distinct neural mechanisms associated with the perceptual processing of human action-related sounds - or even tool-related sounds that are associated with a human action producing them - which have been found to elicit activity in a frontocentral, parietal, and temporal network, while non-human action-related sounds elicit activation of a posterior temporo-parietal network (e.g. Giusti et al., 2010; Hauk, Shtyrov, & Pulvermuller, 2006; Pizzamiglio et al., 2005; Ullsperger et al., 2006) (see also, *Chapter 1, section 1.1.3.4)*.

Repetition suppression refers to the decrease of neural responses as a result of neuronal adaptation and habituation, when stimuli from the same perceptual category are repeated after a short inter-stimulus interval (Baldeweg, 2006; Turk-Browne, Scholl & Chun, 2008). In contrast, when a stimulus is followed rapidly by a stimulus from a different perceptual category, the mean firing rate of neurons increases in response to the new stimulus (Baldeweg, 2006) (see also, *Chapter 2, section 2.2*). In a recent ERP study, Pizzamiglio and colleagues used a cross-modal visual-auditory RS ERP paradigm, in order to examine the neural mechanisms underlying the perceptual processing of action-related sounds in adults (Pizzamiglio et al., 2005). Their ERP paradigm included the presentation of human action (mouth or hand related) and non-human action words and sounds. More specifically, a written human (e.g. clap) or non-human (e.g. fly) action-related visual word was presented to the participants and was followed by a sound produced by either a human action (e.g. hands clapping, ringing a hand bell) or a non-human action (e.g. fly, boiling sound). The authors analysed ERPs from frontal, central, temporal, and temporoparietal channels, and found that human

action processing was associated with activity in the posterior superior temporal and inferior frontal cortices (peak at 280 ms), whereas non-human action sound processing was primarily associated with bilateral temporal activity (peak at 320 ms). These findings provide evidence for a distinctive mechanism for audio-visual human action relative to non-human action processing in adults (Pizzamiglio et al., 2005; see also Galati et al., 2008; Hauk et al., 2006). In addition, Pizzamiglio et al. (2005) findings revealed that incongruent human audio-visual action processing was mostly left lateralised, whereas incongruent non-human audio-visual action processing was bilateral.

Following the Pizzamiglio et al. (2005) study, Giusti et al. (2010) developed both a visual and an auditory RS ERP paradigm, in order to explore further the neural mechanisms associated with the perceptual processing of action-related sounds. Their visual RS paradigm included silent video clips of human action stimuli (hands clapping or banging) and non-human action stimuli (telephone or carillon), whereas their auditory RS paradigm included sound clips produced by the same stimuli (sounds produced by hands clapping or banging and telephone ringing sounds or carillon melodies). The authors found repetition suppression effects in both paradigms and conditions, with action-related sounds eliciting greater activity over left frontal, temporal, and parietal sites (peaks at 170, 235, 385 and 470ms), whereas non-action-related sounds elicited bilateral activity over the temporal and posterior cortices (peak at 160ms) (Giusti et al., 2010). In addition, source estimation analyses revealed evidence for stronger activation of the left hemisphere in response to human action-related stimuli (Giusti et al., 2010), as previously found by Pizzamiglio et al. (2005). These findings provide additional evidence for the existence of distinctive neural functions

associated with visual and auditory human versus non-human action processing (Giusti et al., 2010).

Although previous research has provided evidence for specialist human action sound processing mechanisms in adults (e.g. Giusti et al., 2010; Pizzamiglio et al., 2005), very little is known about the existence of such neural mechanisms in infants and children. Most neuroimaging and electrophysiological auditory processing studies in infants and children have focused on the investigation of specialist brain mechanisms underlying the perceptual processing of human voice and speech (e.g. Ceponiene, Alku, Westerfield, Torki, & Townsend, 2005; Ceponiene, Torki, Alku, Koyama, & Townsend, 2008; Dehaene-Lambertz, Dehaene & Hertz-Pannier, 2002; Grossman et al., 2010; Lloyd-Fox et al., 2013). Interestingly though, in a recent EEG study, Paulus et al. (2012) examined electrophysiological responses and power-changes in the mu frequency band, elicited by familiar action-related sounds, as well as familiar and unfamiliar non-action-related sounds in 8-month-old infants. More specifically, the authors presented three types of auditory stimuli to the infants: a) a sound produced by a human action on a rattle (when shaken), which infants were trained on for one week, b) a non-human action-related sound that infants were also familiarised with, and c) an unfamiliar non-human action sound (Paulus et al., 2012). Although no lateralisation differences were found, the authors reported stronger mu rhythm desynchronization over central channels, as well as over frontal relative to parietal channels, in response to sounds that were previously the effect of the infants' own actions relative to unfamiliar and non-human action related sounds. However, in contrast to this Paulus et al. (2012) finding, in a more recent functional near-infrared spectroscopy study of atypical development in 4- to 6-month old infants, who were at high or low risk of developing a

social and communication disorder, human vocal stimuli, such as sneezing or laughing, were found to elicit greater haemodynamic responses over the right temporal cortex, when compared with toy-related sounds, in low-risk infants (Lloyd-Fox et al., 2013). Together, these findings provide preliminary evidence for the development of a specialist neural mechanism associated with human action sound processing by 8 months of age. However, because the EEG power data in the Paulus et al. (2012) study were collapsed across the entire stimulus presentation window, to date, there have been no reports on the time-course of human versus non-human action sound processing in either infants or young children.

Based on the Pizzamiglio et al. (2005) and Giusti et al. (2010) ERP paradigms previously used with adults, in the current study, we devised an auditory-auditory RS ERP paradigm, in order to investigate the neurodevelopmental trajectory of human action sound processing in toddlers and young children. More specifically, we aimed to investigate whether repetition suppression effects can be elicited by auditory social stimuli in toddlers and young children. We were particularly interested in examinining the nature and time-course of human versus non-human action sound processing in two-year old toddlers and four- to five-year old children, furthering our understanding of any neural processing similarities or differences across these two age groups. The latter were selected based on previous research findings by Sheehan, Namy, and Mills (2007), who employed a match/mismatch ERP paradigm and found an N400 congruency effect in response to gestures only in 18-month old infants as opposed to 26-month olds. These findings may be associated with a "U-shaped" function, which has been reported by previous behavioural research and refers to the developmental regression of symbolic gesture comprehension at two years of age and then an increase again in the

preschool years (Namy, Campbell, & Tomasello, 2004; Sheehan, Namy, & Mills, 2007). A possible explanation for this developmental function has been based on toddlers' tendency to be rigid when they start to distinguish and understand the communicative functions of words and gestures (Namy, Campbell, & Tomasello, 2004). Therefore, the investigation of neural mechanisms associated with human action sound processing in these two age groups will reveal whether similar developmental differences exist on a neurobiological level, in response to sounds associated with human actions, as well.

Aims of the study

The aims of the current study were:

1. to extend previous findings of repetition suppression in adults by examining whether repetition suppression effects are elicited by human and non-human action-related sounds in two different age groups of young children,
2. to investigate whether specialist human action sound processing mechanisms exist in toddlers and young children, as previously found in infants by Paulus et al. (2012),
3. to extend from previous findings by examining the time-course and neurodevelopmental trajectory of human action sound processing in early childhood,
4. to examine the relationship between neural processing of action-related sounds and language development in the toddler participants.

3.2 Method

3.2.1 Sample

Participants were recruited from the Birmingham, West Midlands, region of the United Kingdom, through the distribution of research subject recruitment flyers that were specifically approved by the University of Birmingham Internal Review Board (IRB), and visits at parent groups, play groups for toddlers and young children, local libraries, University social events (e.g. University community day), and other local community events for children and families (e.g. Think Tank Science Museum, Babyshow etc.). Parents, who provided their contact details to the researchers of the Infant and Child Lab at the University of Birmingham, were contacted in order to be informed about studies that would be appropriate for their child's age and developmental level.

As long as parents verbally agreed for their child to take part in the current study, they visited the Infant and Child Lab, where they were asked to read and sign a University of Birmingham Internal Review Board (IRB) approved consent form to approve their child's participation in the study (see *Appendix A1*). Parents were also asked to complete a brief questionnaire and provide information about any medical complications during pregnancy or birth, any issues related to their child's course of physical and neurological development, and/or any medication that was administered to their child (see *Appendix B1*). Premature toddlers or children, or participants who had experienced neurological problems or developmental delays, were excluded from participation in this study. Health-related problems that are not thought to affect a child's brain development, such as allergies, were not considered grounds for dismissal. In addition, bilingual toddlers and children were also excluded from participation.

Thirty-five 2-year-old toddlers (19 males, 16 females) and twenty-five 4- and 5-year old children (15 males, 10 females) participated in the study. Two toddlers were excluded from participation due to developmental delays, reported by parents. One additional toddler was excluded due to preterm birth history, and one further toddler was excluded because he was bilingual. In addition, seven toddlers and one child were excluded from data analyses due to excessive motor and/or ocular motor artifacts in the ERP data. Therefore, the current analyses are based on ERP data from 24 toddlers (14 males, 10 females) and 24 children (14 males, 10 females). The mean chronological age of the final sample of toddlers was 29 months (S.D. = 3.8) and the mean age of the final sample of children was 58 months (S.D.= 5.9) (see *Table 2*). Parents of all child participants that were included in the current analyses were also asked to provide information relating to their children's handedness. Eighteen children were determined to be right-handed, whereas six children were left-handed.

3.2.2 Behavioural measures

A behavioural measure utilised in this study was the language ability-screening questionnaire, the MacArthur-Bates Communicative Development Inventory: Words and Sentences (CDI-II; Fenson et al., 1993), which was completed by parents of toddler participants (see also, *Table 2*). The CDI-II (Fenson et al., 1993) is a standardised and reliable measure of language skills in this age range and has been used extensively in previous research. The CDI-II was used in order to explore the relationship between action-related sound neural processing and language development at two years of age.

Group	N	Gender	Chronological age (months)	CDI-II (number of words)
Toddlers	24	14 males, 10 females	29 (3.8)	453 (145.5)
Children	24	14 males, 10 females	58 (5.9)	N/A

Table 2. *Characteristics of toddler and child groups - Means and standard deviations (S.D.).*

3.2.3 Stimuli- Experimental procedure

The ERP assessment utilised in the present study involved a novel auditory-auditory RS ERP paradigm that included a single block of approximately 570 trials, lasting for 30 minutes and presenting two types of sounds: human action (i.e., hands clapping, hands ripping paper) and non-human action (i.e., helicopter blades spinning, ocean waves) -related sounds. Each type of sound was followed by a sound from either the same or the other perceptual category, resulting in four trial types: a) congruent (repeated) human action-related sound trial, b) incongruent (non-repeated) human action-related sound trial, c) congruent (repeated) non-human action-related sound trial, and d) incongruent (non-repeated) non-human action-related sound trial (see also, *Chapter 2, Sections 2.3, 2.4*).

3.2.4 ERP Recording and Analysis

Brain electrical activity was recorded continuously using a child-friendly, high-density, 128-channel Hydrocel Geodesic Sensor Net (HCGSN, Electrical Geodesics Inc., Eugene, Oregon) (Tucker, 1993). EEG was referenced to a single vertex electrode,

Cz (sample rate = 500 Hz). All bioelectrical signals were recorded using EGI NetStation amplifiers with an input impedance of less than 100 kΩ.

EEG data were band-pass filtered offline at 0.1 to 40 Hz and segmented to epochs, using NetStation 4.2 software (Electrical Geodesics, Inc., Eugene, Oregon). Epochs were time-locked to the second auditory stimulus in the trial, contained 100 ms pre-stimulus time and 700 ms post-stimulus time, and were organised by stimulus type [human action sound repetition (congruent), human action sound non-repetition (incongruent), non-human action sound repetition (congruent), non-human action sound non-repetition (incongruent)]. Data were then processed using an artifact-detection tool, which marked channels bad, if the recording was poor for greater than 99 % of the time (threshold maximum-minimum, >150), and segments, if they contained more than 12 bad channels, eye-blinks, or eye-movements. Following this automated artifact detection process, individual examination of each of the trials was also performed by a trained EEG researcher in order to remove trials including any remaining ocular or motor artifacts from the data. All toddlers and children produced a minimum of 40 viable ERP trials per experimental condition. *Table 3* shows the means and standard deviations (S.D.) of motor and ocular-motor artifact-free trials per condition, per group. Independent samples t-tests revealed that the numbers of artifact-free trials per condition were not significantly different between the groups: a) congruent human action sound trials (Toddlers: M=62.8, S.E.=3.35, Children: M=71, S.E.=2.92), $t(46)=-1.86$, $p>0.05$, b) incongruent human action sound trials (Toddlers: M=64.5, S.E.=3.62, Children: M=69.3, S.E.=3.14), $t(46)=-1.02$, $p>0.05$, c) congruent non-human action sound trials (Toddlers: M=63.4, S.E.=3.47, Children: M=67, S.E.=2.95), $t(46)=-0.81$, $p>0.05$, and d) incongruent non-human action sound trials (Toddlers: M=64.7,

S.E.=3.38, Children: M=67.7, S.E.=2.91), $t(46)=-0.68$, $p>0.05$, equal variances assumed. Trials containing 12 or fewer bad channels were included in the current analyses and data for those bad channels were replaced using a spherical spline interpolation algorithm (Srinivasan, Nunez, Tucker, Silberstein, & Cadusch, 1996). Finally, individual subject data were averaged, re-referenced to an average reference, and baseline-corrected to a 100 ms pre-stimulus interval.

Group	**Human-action sound trials**		**Non-human-action sound trials**	
Condition	*Congruent*	*Incongruent*	*Congruent*	*Incongruent*
Toddlers	62.8 (16.4)	64.5 (17.7)	63.4 (17)	64.7 (16.6)
Children	71 (14.3)	69.3 (15.4)	67.1 (14.5)	67.7 (14.3)

Table 3. *Descriptive data - Means (S.D.) of artifact-free trials per condition in toddler and child groups.*

Electrode locations and time windows for analysis in the current study were selected based on previous ERP findings of human action and gesture processing studies in infants, children, and adults (e.g. Giusti et al., 2010; Paul et al., 2012; Pizzamiglio et al., 2005; Sheehan, Namy, & Mills, 2007), and on visual inspection of grand average ERP data, prior to any statistical analysis. Electrode sites that were selected for analysis included 33 frontal and frontocentral (11 left, 11 middle, 11 right), 14 temporal (7 left, 7 right), and 24 parietal (8 left, 8 middle, 8 right) electrodes (see *Figure 3*). Averaged ERPs obtained during all experimental conditions were analysed

sample by sample in the 40-700 ms temporal window by using repeated-measures Analysis of Variance (ANOVA), paired contrasts and one sample *t*-tests, in order to identify any repetition suppression effects in response to human action versus non-human action-related sounds. A Bonferroni correction was also employed. Different time windows for human and non-human action sound processing over frontal, temporal and parietal electrode sites were selected for analysis. The mean amplitude of the major ERP components was compared between conditions and groups. In addition, the peak latency of some of the components was also analysed, in order to examine timing processing differences between the younger and the older groups. Although the same time windows were selected for analysis in both toddlers and children, both within- and between-subjects analyses were conducted, in order to explore potential neurodevelopmental differences across the age groups.

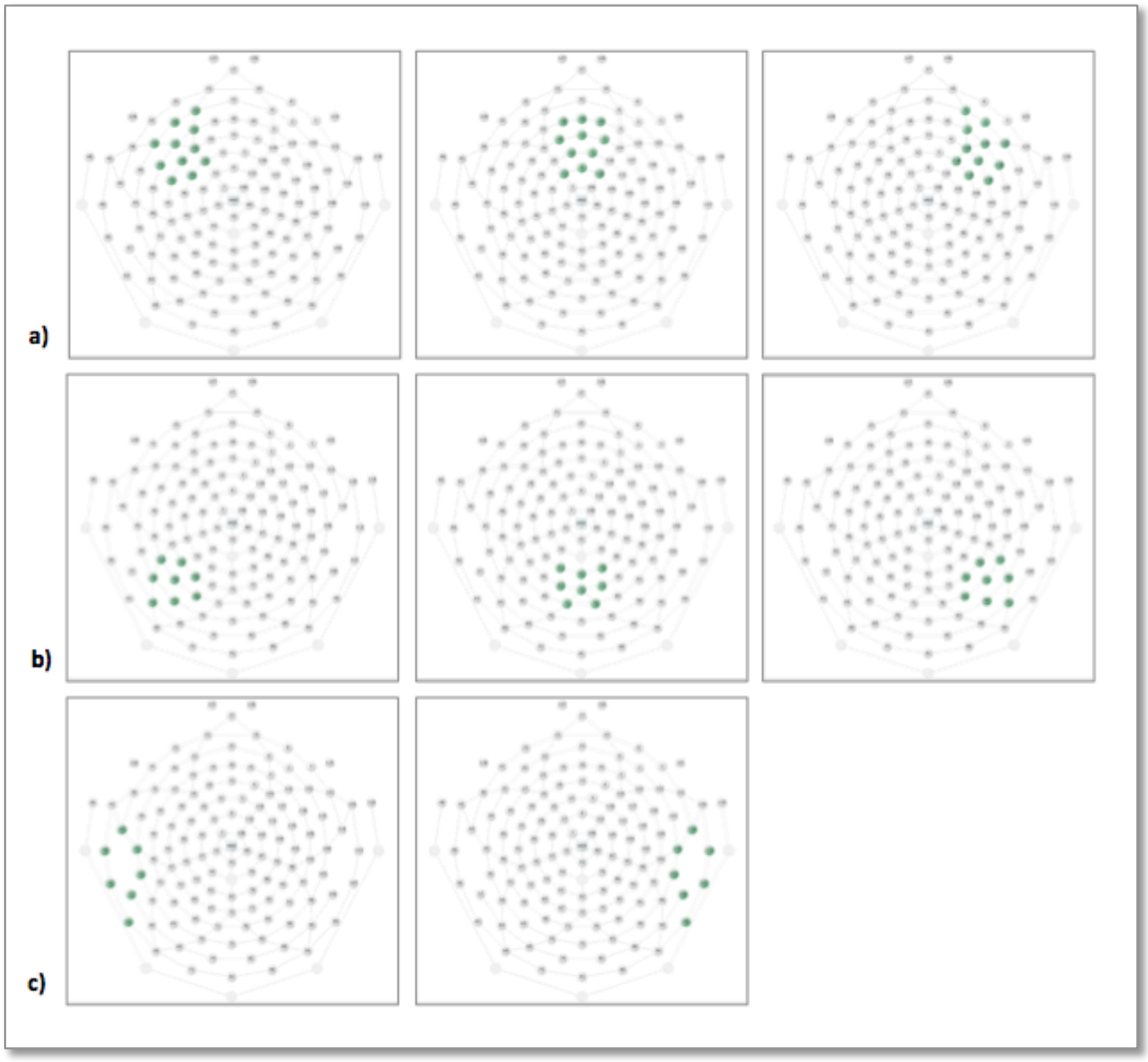

Figure 3. *Montage selected for analysis in typically developing toddlers and children.*

a) Left, middle and right frontal electrodes selected for the ERP data analyses. b) Left, middle and right parietal electrodes selected for the ERP data analyses, and c) Left and right temporal electrodes selected for the ERP data analyses.

3.3 Results

ERPs to human action sounds included two early sensory processing components (P1, N1), two early components reflecting stimulus feature mismatch cortical responses (P2, N2), and three later perceptual processing components reflecting stimulus category mismatch cortical responses (P3, N4, N600). ERPs to non-human action sounds

included the P1 and N1 components. P1 (40-170ms) peaked at approximately 100 ms over the frontal and frontocentral channels, whereas N1 was identified within the same time window over the temporal and parietal sites. P2 and N2 components were identified within the time window 180-300 ms over the frontal and parietal cortex, respectively. P3 component was identified within the time window 400-530 ms and peaked at approximately 460 ms over the temporal sites. Finally, N4 (400-530ms) and N600 (540-670ms) components were identified over the frontal region. Mean amplitude analysis was carried out on all ERP components, whereas peak latency analysis was carried out only on P1, N1 and N4.

A between-subjects, repeated-measures ANOVA with stimulus type (human action sound, non-human action sound), condition (congruent / repeated stimuli, incongruent / non-repeated stimuli) and hemisphere (left, middle, right) as within-subjects factors, and group (toddlers, children) as between-subjects factor, was carried out on the mean amplitude and peak latency of the selected components. However, only interactions between stimulus type and condition, revealing a significant repetition suppression effect, were considered for follow-up analyses, which included pairwise comparisons using Bonferroni correction and one-sample t-tests. In addition, the relationship between cortical responses to both human and non-human action sounds and language ability in toddlers was explored by conducting correlation analyses between the mean amplitude and peak latency of the selected components and the number of words used by toddlers, as reported on the CDI-II. However, given the relatively small sample in the present study, the results from this correlation analysis were viewed with caution.

Frontal activity

P1 (P100: 40-170ms)

A stimulus type (human action sound, non-human action sound), by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (toddlers, children) repeated-measures ANOVA was carried out on the P1 mean amplitude. Mauchly's test indicated that the assumption of sphericity was violated for the interaction between stimulus type, condition and hemisphere. Therefore, degrees of freedom were corrected by using Greenhouse-Geisser estimates of sphericity (ε=0.83). The analysis revealed a significant effect of condition (F(1,46)=12.17, p=0.001), a significant interaction between stimulus type and condition (F(1,46)=25.67, p<0.001), and a significant interaction between stimulus type, condition and hemisphere (F(1.66,76.13)=5.44), p<0.05. Paired contrasts using Bonferroni correction showed that this interaction was driven by greater P1 responses to non-repeated non-human action sounds over the middle relative to left frontal channels, p<0.05. However, no significant differences were found between middle and right (p=0.26) or between left and right frontal activity (p=1.00). A one-sample t-test also revealed that the amplitude of these P1 responses was significantly different from 0, t(47)=11.86, p<0.001 (see *Figure 4*).

A stimulus type (human action sound, non-human action sound), by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (toddlers, children) repeated-measures ANOVA on the peak latency of the P1 revealed no significant effects or interactions.

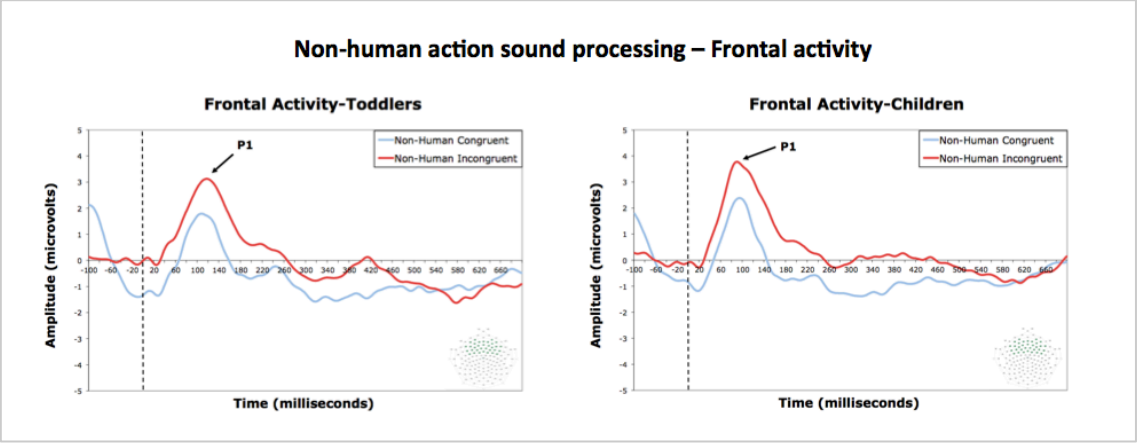

Figure 4. *Repetition suppression waveforms recorded over the frontal and frontocentral channels for non-human action sounds in toddlers and children.*

P2 (P240: 180-300ms)

A stimulus type (human action sound, non-human action sound), by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (toddlers, children) repeated-measures ANOVA was carried out on the P2 mean amplitude and revealed a significant effect of stimulus type ($F(1,46)=16.59$, $p<0.001$), as well as a significant interaction between stimulus type and condition ($F(1,46)=11.92$, $p=0.001$). According to paired contrasts using Bonferroni correction, this interaction was driven by larger P2 responses to repeated human action sound relative to non-human action sound stimuli, $p<0.001$. One-sample t-tests on P2 responses in the congruent human action sound condition was also found to be significant, $t(47)=-8.15$, $p<0.001$) (see *Figure 5*).

N4 (N460: 400-530ms)

A stimulus type (human action sound, non-human action sound), by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (toddlers,

children) repeated-measures ANOVA was carried out on the N4 amplitude. Mauchly's test indicated that the assumption of sphericity was violated for the interaction between stimulus type, condition and hemisphere. Therefore, degrees of freedom were corrected by using Greenhouse-Geisser estimates of sphericity (ε=0.77). The analysis revealed a significant interaction between stimulus type and condition (F(1,46)=14.93, p<0.001), and a significant interaction between stimulus type, condition, hemisphere and group (F(1.54,70.99)=3.54, p<0.05). Pairwise comparisons using Bonferroni correction showed that this interaction was driven by larger cortical responses to non-repeated versus repeated human action sounds over the middle and right frontal channels in the toddler group, p<0.05. One sample t-tests also showed that these responses were significantly different from 0, t(23)=-2.5, p<0.01 (see *Figures 5, 6*). Repeated analyses of variance on the N4 peak latency did not reveal any significant main effects or interactions.

N600 (540-670ms)

A stimulus type (human action sound, non-human action sound) by condition (congruent, incongruent) by hemisphere (left, middle, right) by group (toddlers, children) repeated-measures ANOVA was carried out on the mean amplitude of N600. Mauchly's test indicated that the assumption of sphericity was violated for the interaction between stimulus type, condition and hemisphere. Therefore, degrees of freedom were corrected by using Greenhouse-Geisser estimates of sphericity (ε=0.75). The analysis revealed a significant effect of condition (F(1,46)=9.46, p<0.01), a significant interaction between stimulus type and condition (F(1,46)=8.87, p<0.01), and a significant interaction between stimulus type, condition, hemisphere and group

($F(1.51,69.35)=3.46$, $p=0.05$). In accordance with N4 mean amplitude analysis, paired contrasts using Bonferroni correction showed that this interaction was driven by greater responses to non-repeated relative to repeated human action sounds over the middle ($p<0.05$) and right ($p<0.01$) frontal channels in the toddler group. One sample t-tests showed that these responses were significantly different from 0, $t(23)=-3.28$, $p<0.01$ (see *Figure 5*).

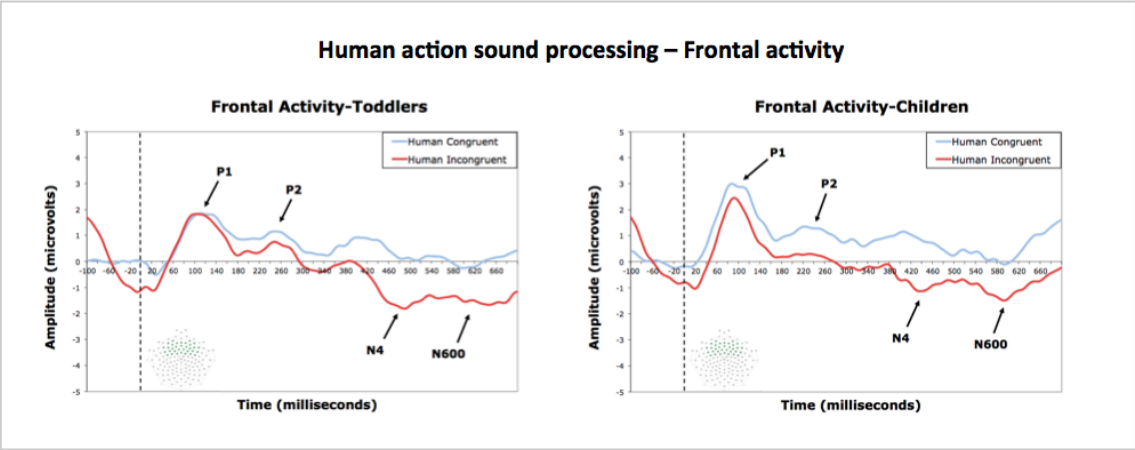

Figure 5. *Repetition suppression waveforms recorded over the frontal and frontocentral channels for human action sounds in toddlers and children.*

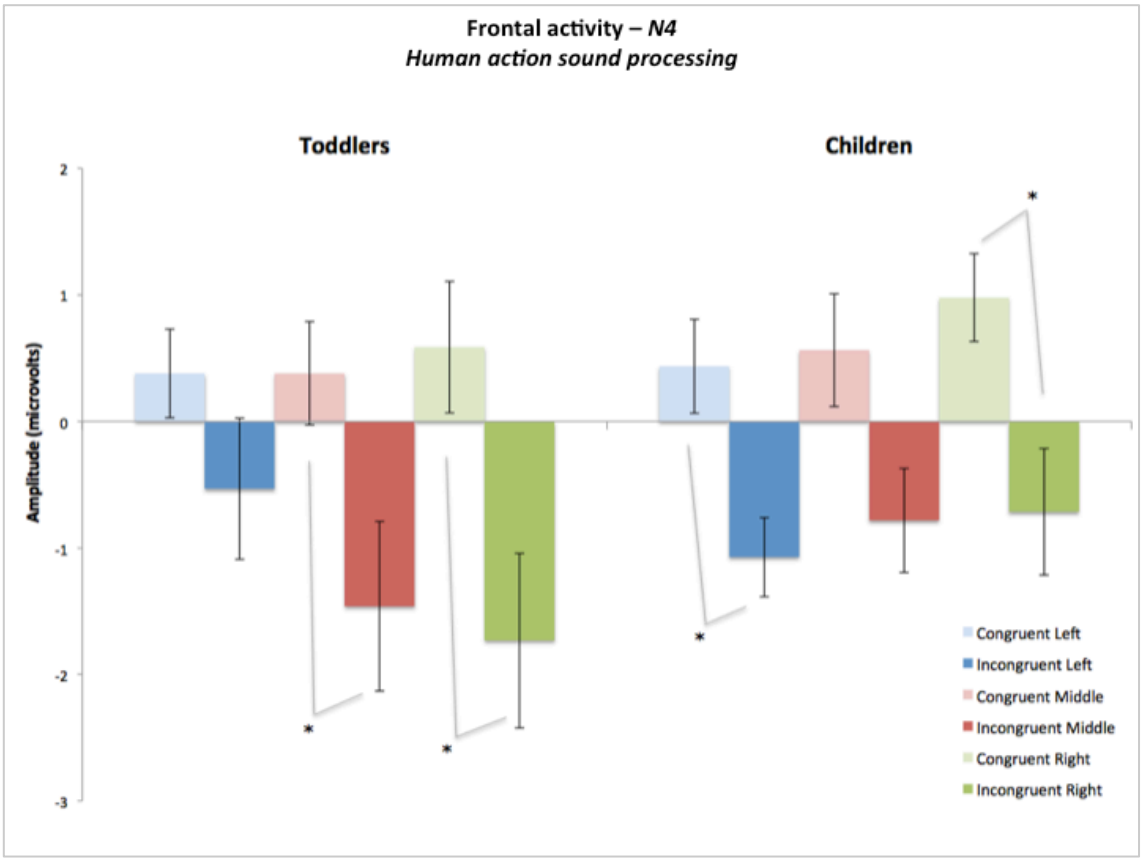

Figure 6. *N4 mean amplitude in response to repeated and non-repeated human action sounds over the left, middle and right frontal cortex in toddlers and children.*

Temporal activity

N1 (N100: 40-170ms)

A repeated-measures ANOVA with stimulus type (human action sound, non-human action sound), condition (congruent, incongruent) and hemisphere (left, right) as within-subjects factors, and group (toddlers, children) as between-subjects factor, was carried out on the N1 mean amplitude and revealed a significant interaction between stimulus type and condition, $F(1,46)=15.62$, $p<0.001$. Paired contrasts using Bonferroni correction showed that this interaction was driven by greater N1 responses to non-repeated relative to repeated non-human action sounds over temporal channels,

p<0.001. A one-sample t-test revealed that the latter were significantly different from 0, t(47)=-8.15, p<0.001 (see *Figure 7*).

A stimulus type (human action sound, non-human action sound) by condition (congruent, incongruent), by hemisphere (left, right), by group (toddlers, children) repeated-measures ANOVA on the peak latency of N1 revealed no significant effects or interactions.

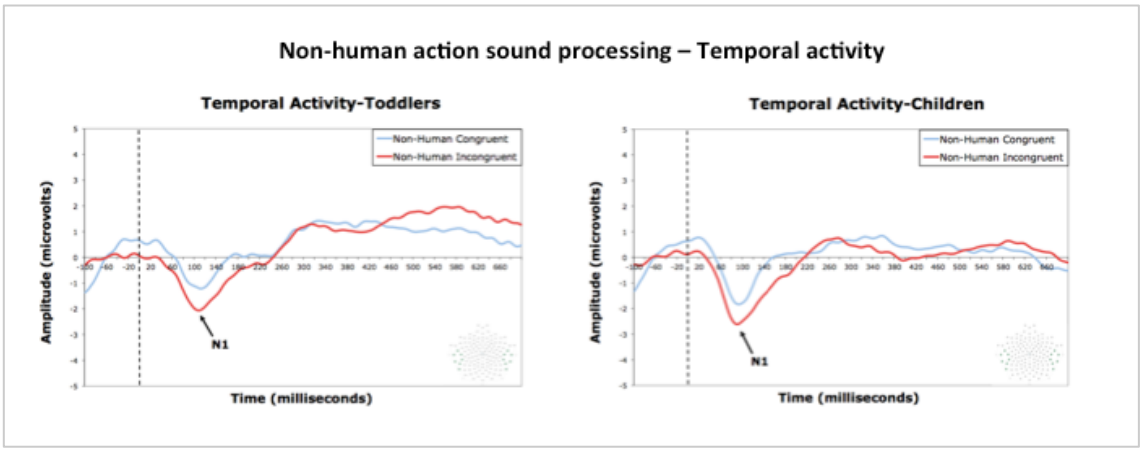

Figure 7. *Repetition suppression waveforms recorded over the temporal cortex for non-human action sounds in toddlers and children.*

P3 (P460: 400-530ms)

A stimulus type (human action sound, non-human action sound), by condition (congruent, incongruent), by hemisphere (left, right), by group (toddlers, children) repeated-measures ANOVA revealed a significant effect of condition (F(1,46)=7.85, p<0.01), and a significant interaction between stimulus type and condition (F(1,46)=6.86, p<0.05). Paired contrasts using Bonferroni correction revealed that this effect was driven by larger P3 responses to non-repeated versus repeated human action sound stimuli in both age groups, p<0.001. A one-sample t-test also showed that P3

amplitude to non-repeated human action sound stimuli was significantly different from 0, $t(47)=4.19$, $p<0.001$ (see *Figure 8*).

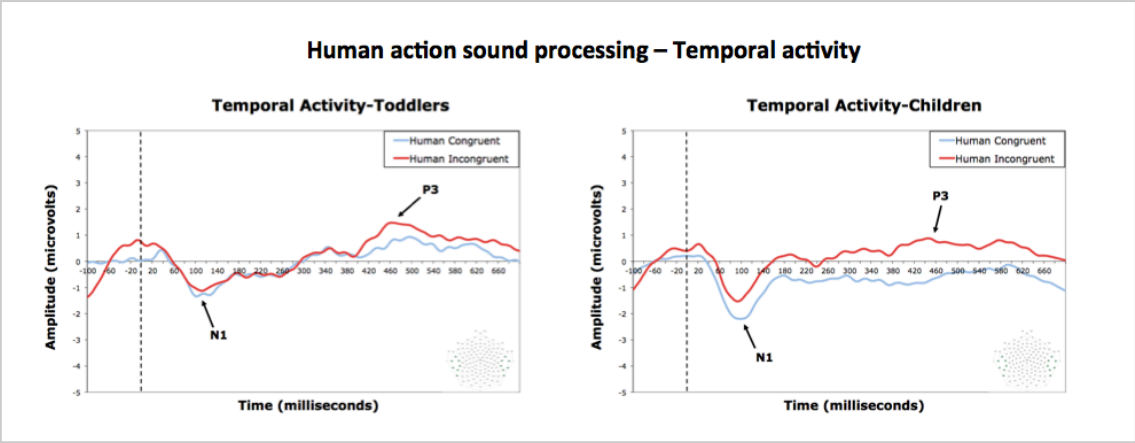

Figure 8. *Repetition suppression waveforms recorded over the temporal cortex for human action sounds in toddlers and children.*

Parietal activity

N1 (N100: 40-170ms)

A stimulus type (human action sound, non-human action sound) by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (toddlers, children) repeated-measures ANOVA on the mean amplitude of N1 revealed no significant main effects or interactions.

A stimulus type (human action sound, non-human action sound) by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (toddlers, children) repeated analyses of variance on the peak latency of N1 revealed a significant effect of stimulus type ($F(1,46)=5.07$, $p<0.05$), and a significant interaction between stimulus type, condition and group ($F(1,46)=5.26$, $p<0.05$). Paired contrasts using Bonferroni correction showed that this interaction was driven by slower responses to

repeated human action sounds (p<0.05) and to non-repeated non-human action sounds (p<0.01) over the parietal channels in toddlers, when compared with children (see *Figures 9, 10, 11*). In addition, a significant negative correlation between the N1 peak latency to repeated human action sounds and chronological age (r=-.66, p<0.001), as well as between the N1 peak latency to repeated human action sounds and language ability (number of words on the CDI-II), when controlling for chronological age, was found in the toddler group, r=-.55, p<0.01. The same negative relationship was also found between the N1 peak latency to non-repeated non-human action sounds and language ability, when controlling for age, r=-.45, p<0.05.

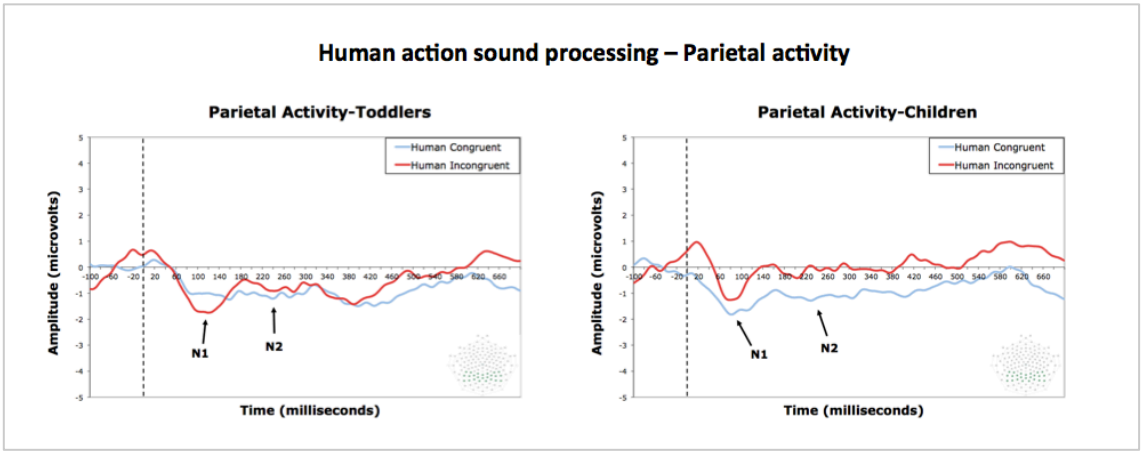

Figure 9. *Repetition suppression waveforms over the parietal cortex for human action sounds in toddlers and children.*

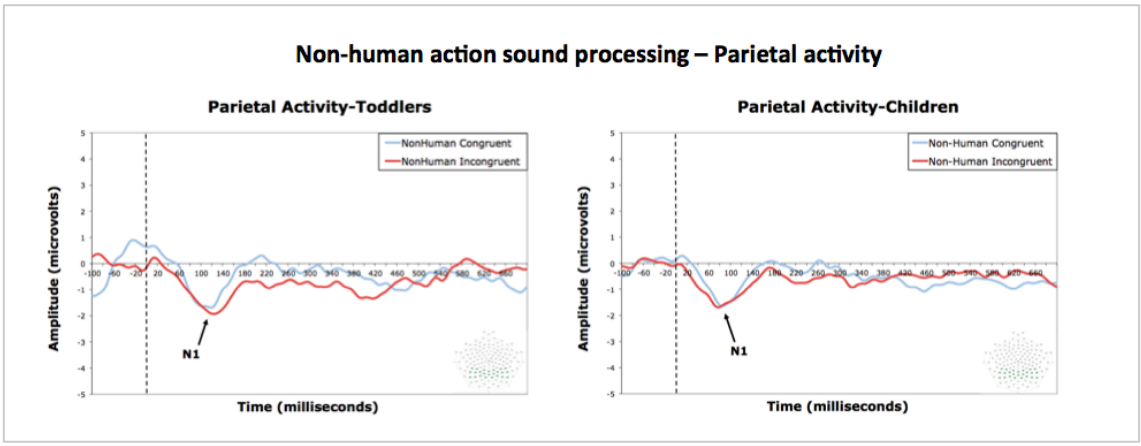

Figure 10. *Repetition suppression waveforms recorded over the parietal cortex for non-human action sounds in toddlers and children.*

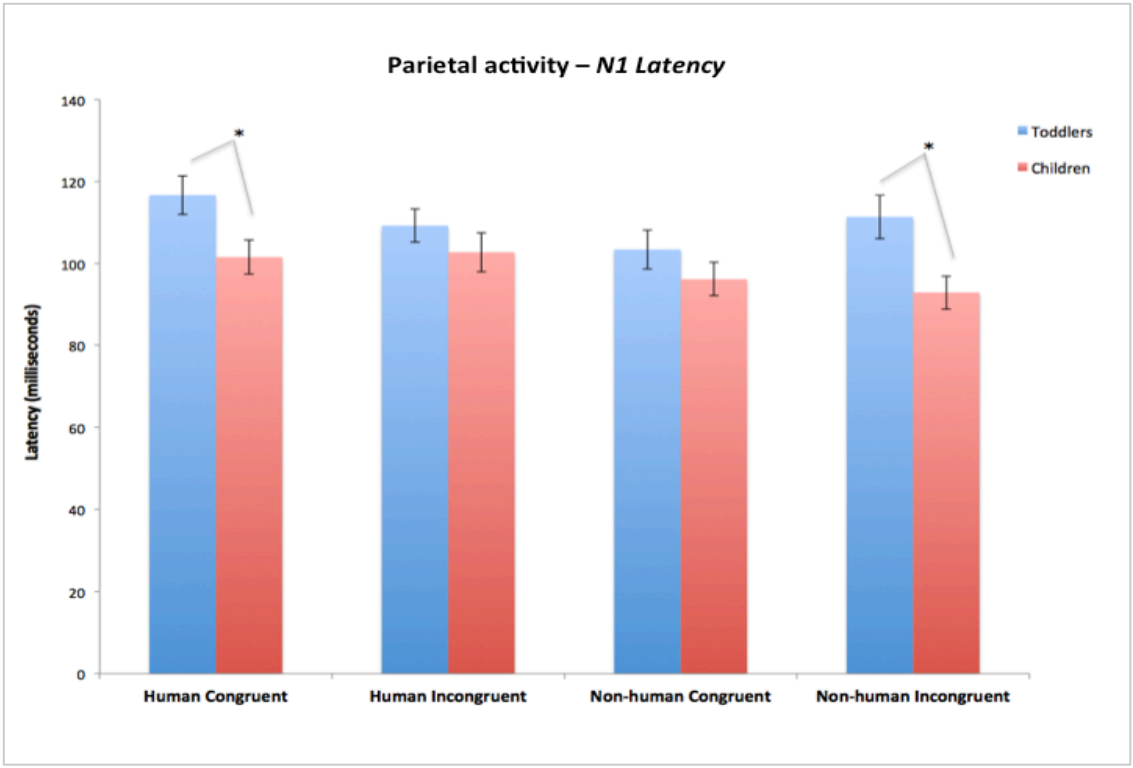

Figure 11. *N1 peak latency in response to repeated and non-repeated human and non-human action sounds over the parietal cortex in toddlers and children.*

N2 (N240: 180-300ms)

A stimulus type (human action sound, non-human action sound), by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (toddlers, children) repeated-measures ANOVA revealed a significant interaction between stimulus type and condition, $F(1,23)=5.85$, $p<0.05$. Paired contrasts using Bonferroni correction showed that this interaction was driven by a larger N2 mean amplitude to repeated versus non-repeated human action sound stimuli, $p<0.05$. A one-sample t-test also showed that N2 amplitude to repeated human action sound stimuli was significantly different from 0, $t(47)=-5.24$, $p<0.001$ (see *Figure 9*).

3.4 Discussion

In the current study, we utilized event-related potentials in order to explore the nature, time-course, and neurodevelopmental trajectory of the neural mechanisms of human action sound processing in early childhood. The ERP findings observed provide evidence for the existence of specialised neural mechanisms underlying human and non-human action sound processing by two years of age. Repetition suppression effects to both human and non-human action sounds were found in both toddler and child groups. Notably, however, non-human action sounds elicited only early sensory processing ERP components (P1, N1) over the frontal, frontocentral, and temporal channels, whereas human action sound processing was associated with both early (P1, N1, P2, N2) and later perceptual processing ERP component activity (P3, N4, N600) over the frontal, frontocentral, temporal, and parietal sites in both age groups. In addition, significant lateralisation differences for human action sound processing were observed between the

age groups during the late stages of cognitive processing, with N4 and N600 frontal components being right lateralised in toddlers, but bilateral in children.

The results of the current study replicate previous ERP findings in neurotypical adults showing repetition suppression effects in response to both human and non-human action-related sounds (Giusti et al., 2010; Pizzamiglio et al., 2005). In addition, they extend previous EEG findings of specialised human action sound processing mechanisms in infants (Paulus et al., 2012) by providing evidence for the time-course and development of these mechanisms from 2 to 5 years of age. Moreover, the current data suggest the existence of "predictive coding" neural mechanisms for auditory social stimuli in young children, extending previous ERP findings of repetition suppression effects in response to visual social stimuli (faces versus objects) in 6-month old infants (Snyder and Keil, 2008).

In terms of the neural time-course of action- and non-action-related sound processing, the present study demonstrated that distinct neural mechanisms associated with human versus non-human action sound processing develop within the first two years of age. In accordance with previous ERP findings in adults by Giusti and colleagues (2010), the current results reveal both early sensory and later perceptual processing stages for human action sounds, whereas non-human action sounds elicited only the early P1 and N1 components. This pattern of ERP time-course was also reported by Murray et al. (2006), who used an "oddball" target detection task and found that object sounds (e.g., musical instruments, car horn, telephone) elicited larger early frontal and temporal activity in adults, whereas sounds of living objects (e.g., animal sounds, baby crying, sneezing) were associated with prolonged activity over the premotor and temporal regions at a later stage of processing. The P1 and N1

components observed in the current study were driven by larger cortical responses to non-action-related sounds (peak at 100ms) over the frontal and temporal cortices and are similar to the P160 and P150 components that have been revealed in response to deviant auditory non-social stimuli by previous studies using repetition suppression and mismatch negativity experimental designs in adults and infants, respectively (Giusti et al., 2010; Guiraud et al., 2011). In addition, in accordance with Giusti et al. (2010) and Pizzamiglio et al. (2005) findings in adults, no significant differences were found between the left and right frontal cortex for non-human action sound processing, although there was a trend for larger P1 responses over the middle frontal region. This finding may reflect a developmental ERP effect associated with environmental sound processing in early childhood, and needs further investigation. In addition, although no significant effects or interactions were revealed for the mean amplitude of N1 over the parietal sites, the N1 peak latency was found to be delayed in response to non-repeated non-human action sounds in toddlers relative to children, providing preliminary evidence for differential non-human action processing mechanisms across these age groups.

Differences in repetition suppression neural mechanisms between toddlers and children were revealed with respect to human action sound processing, as well. For example, the parietal N1 peak latency was found to be delayed for repeated human action sounds in toddlers, when compared with the older group. Interestingly, this delay was observed to be negatively correlated with both chronological age and language ability measured through CDI-II in toddlers. A similar negative correlation was also found for the incongruent non-human action sound condition mentioned above. These results may reflect a relationship between the latency of early sensory processing of

auditory social and non-social stimuli and expressive language ability. More specifically, as larger P1 and N2 amplitudes have been found to be elicited by repeated speech stimuli of different complexity or sensory properties in school-age children (Ceponiene et al., 2003), this relationship may reflect a correlation between sensory processing of changes in physical features of auditory social stimuli and language development; however, it should be viewed with caution due to the relatively small group of toddlers included in the current study. Similarly, within a second early stage of processing in the present results, P2 and N2 component activity was identified over the frontal and parietal channels, respectively, and both of them were found to be larger in response to repeated human action sounds, which, however, were not identical. This effect may reflect differences in processing of changes in sensory properties of human versus non-human action sounds, and provides additional evidence for the development of distinct action-related sound neural processing mechanisms in toddlers and young children.

In terms of the perceptual processing of human action sounds, we expected to find larger cortical responses to non-repeated human action sounds, which would reflect the release of neural mechanisms in response to the presentation of stimuli from a differential perceptual category. In fact, cognitive processing of action-related sounds was identified within the time window 400-530ms over the frontal (N4) and temporal (P3) cortices, as well as within the time window 540-670ms (N600) over the frontal cortex. More specifically, greater activity was elicited by human action sounds following object or environmental sounds for all the late components. P3 has been considered to be an index of attentional orienting to novel, perceptually salient stimuli, and has been previously found in both adults (e.g. Escera, Alho, Winkler, & Naatanen,

1998; Escera, Yago, & Alho, 2001) and children (e.g. Ceponiene et al., 2003; Kilpelainen et al., 1999). In accordance with previous studies showing significant P3 effects in response to changes in speech sounds in children (e.g. Ceponiene et al., 2003), in the current study, P3 responses were found to be significantly larger in response to novel sounds that were produced by human actions relative to environmental or object sounds. Similarly, frontal N4 and N600 responses were elicited only by novel action-related sounds following object or environmental sounds, reflecting higher levels of neural firing in response to stimuli from a novel social stimulus category.

Although no correlation was observed between N4 mean amplitude or peak latency and language ability in the present study, the N4 was similar to the N400 component reported by previous studies investigating speech repetition effects in infants and adults (e.g. Dehaene-Lambertz & Dehaene, 1994; Kim et al., 2006) and gesture processing in toddlers and young children (Sheehan, Namy and Mills, 2007), and it is associated with stimulus categorisation and violation of semantic expectancy (see also Sheehan, Namy and Mills, 2007). For example, Dehaene-Lambertz and Dehaene (1994) reported a syllable repetition effect at approximately 400 ms in 3-month old infants, which was found to be associated with phonological perception rather than acoustical discrimination of syllables. Similarly, Sheehan, Namy, and Mills (2007) found N400 congruency effects for both words and gestures in 18-month old toddlers, but only for words in 2-year old toddlers. Notably, in the current study, neurodevelopmental differences between the age groups were observed only in relation to lateralisation within late stages of cognitive processing. More specifically, N4 and N600 repetition suppression effects were significant only over the middle and right frontal regions in toddlers, whereas children exhibited bilateral frontal RS activity. These findings do not

support previous research in 8-month old infants by Paulus et al. (2012), who did not find any lateralisation differences in response to a toy sound that was produced by a human action. However, in another fNIRS study, Lloyd-Fox et al. (2013) reported greater haemodynamic responses specifically over the right temporal cortex in response to non-speech vocalizations in 4- to 6-month old infants. These lateralisation differences found in the aforementioned studies in infants may be associated with differences in types of stimuli used by Paulus et al. (2012) and Lloyd-Fox et al. (2013) (hand actions versus vocalisations). Similarly, Paulus and colleagues (2012) used only sounds produced by an action on an object, although sounds utilised in the current study included both a simple hand action sound (hands clapping) and a sound produced by a hand action on an object (ripping paper).

On the other hand, right lateralisation of human action sound processing found in toddlers in the present study may also reflect a distinct, chronological age related neural processing mechanism, which may be different from bilateral or left-lateralised action-related processing mechanisms previously reported in infants (Paulus et al., 2012) and adults (Giusti et al., 2010; Pizzamiglio et al., 2005), respectively. In addition, greater activity in response to human action-related sounds over the right hemisphere in toddlers, as opposed to children who presented with bilateral frontal activity, may reflect higher levels of attention to sounds associated with human actions versus object/environmental sounds in the toddler group. For example, a speech processing fMRI study in 3-month old infants revealed greater activity over the right prefrontal cortex only when the infants were awake (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002). This hypothesis may also be associated with previous behavioural and ERP findings in toddlers and young children demonstrating a decrease in gesture

comprehension from 18 months to two years of age, and an increase again by 4 years of age (Namy, Campbell, & Tomasello, 2004; Sheehan, Namy & Mills, 2007). Namy et al. (2004) suggested that this U-shaped function may be related to a period of time in early childhood, when toddlers begin to understand the communicative functions of words and gestures, and differentiate them. However, the relationship between perceptual processing of human action-related sounds and the U-shaped function of gesture comprehension previously found in toddlers needs further investigation, through the use of gesture and language behavioural assessments and the examination of the relationship between children's behavioural performance and ERP activity, for example. Furthermore, the N4 lateralisation differences observed across the age groups in the current study should be interpreted with caution, given that no information about handedness was available from parents of toddlers, although a hand preference may start to develop by two years of age (Nelson, Campbell, & Michel, 2013). However, it is unknown whether this hand preference would be stable for all toddler participants until 4 or 5 years of age.

Although the present findings extend previous findings of neuronal adaptation to human versus non-human action-related sounds in adults by demonstrating similar repetition suppression effects for both human and non-human action sounds in toddlers and young children, it is important to note a few limitations relating to the methods employed. First, only two types of stimuli from each perceptual category (human versus non-human) were selected for the auditory repetition suppression ERP paradigm used in the present study. Although this selection has been justified in the methods section, a larger range of human action sound stimuli would be helpful in order to develop a better understanding of action sound processing in early childhood. Second, in the present

repetition suppression ERP paradigm, epochs were time-locked to the second auditory stimulus in each trial and only cortical responses to the second stimuli were examined. However, the comparison of ERPs elicited by the second stimulus with those elicited by the preceding one would contribute to a more robust ERP assessment of repetition suppression brain mechanisms. Third, as some of the cartoon videos used in the present study in order to entertain the children included human actions, it would be interesting to replicate the current findings using standard non-social videos for all participants and compare the results to the current findings. Alternatively, the use of social videos for the investigation of visual processing of actions, followed by the use of the same videos during the auditory processing ERP assessment would allow us to distinguish ERPs associated with visual processing of actions and to examine whether and how these might interfere with auditory processing of action-related sounds. Finally, as this is the first study to provide evidence for human and non-human action sound processing mechanisms in young children, the current findings need to be replicated, and larger samples should be tested in future studies aiming to examine relationships of brain and behavioural development.

Further suggestions for future research include the replication of the present findings by using pairs of different sounds from the same perceptual category (human action sound followed by a different human action sound). Although previous findings in adults revealed no significant perceptual processing differences between cortical responses to pairs of the same sounds and pairs of different sounds from the same perceptual category (Giusti et al., 2010), it would be interesting to investigate if this stimulus categorisation and habituation effect develops by early childhood. In addition, the separation and direct comparison of neural activity elicited by sounds produced by

simple hand actions versus sounds produced by actions involving objects might contribute to a better understanding of previous conflicting findings in terms of the lateralisation of action-related sound processing in infants. Finally, the investigation of the relationship between human action sound processing and verbal and non-verbal abilities by using standardised behavioural measures in young children may also enrich our knowledge with respect to the relationship between action or gesture comprehension and language or motor development.

In sum, the present study is the first ERP study to explore the specific nature and time-course of human versus non-human action sound processing in early childhood, and to further examine its development from toddlers to young children. Notably, human action sounds elicited both early sensory cortical responses, and slower brain activity within later stages of cognitive processing, whereas environmental or object sounds elicited neural activity only within early stages of sensory processing. Furthermore, the comparison of two different age groups revealed developmental differences, especially for human action sound processing, between 2-year old toddlers and 4- to 5-year old children, with toddlers showing slightly slower parietal activity at the early stages of sensory processing. However, they exhibited greater repetition suppression effects over the middle and right frontal regions at later stages of cognitive processing, when compared with 4- and 5-year old children.

The current findings contribute to a growing body of evidence for the existence of specialist neural mechanisms for the processing of other people and their actions early in human development. The examination of these mechanisms may have future implications not only for the understanding of language and social development in typically developing children; it may also have clinical implications for the

understanding of social development in individuals with communication and social interaction difficulties, such as individuals with autism, who have been found to exhibit atypical visual processing of human actions (e.g., Oberman, Hubbard, McCleery et al., 2005; Kaiser et al., 2010a; Kaiser & Pelphrey, 2012).

CHAPTER 4:

HUMAN AND NON-HUMAN ACTION SOUND PROCESSING IN YOUNG CHILDREN WITH AUTISM SPECTRUM DISORDERS AND TYPICALLY DEVELOPING CHILDREN

Abstract

Background: Previous behavioural and neuroimaging studies have revealed reduced attention to social orienting cues, such as eye-gaze and pointing gestures, as well as atypical visual perceptual processing of biological motion and human actions in children with autism spectrum disorders. However, it is not currently known whether these atypicalities are confined to the perceptual processing of visual social stimuli or, instead, also extends to social processing in the auditory modality. The aim of the current study was to examine perceptual processing of human action-related sounds in 4- to 6-year old high-functioning children with ASD. **Method:** An auditory-auditory repetition suppression event-related potentials (ERPs) paradigm was employed such that ERPs were recorded while children with ASD and typically developing controls, matched for gender, chronological age, and verbal ability, passively listened to repeated or non-repeated human action or non-human action sounds. **Results:** ERPs over frontal and temporal electrode sites did not differ between the groups for either type of sound. However, children with ASD exhibited enhanced processing of non-human action sounds over posterior parietal sites, when compared with control participants. In addition, children with autism exhibited less habituation to human-action sounds at a later stage of cognitive processing over the same parietal electrode sites. **Conclusion:** These results extend previous findings of impaired visual action processing mechanisms into the auditory modality in children with ASD. They further support the hypothesis that ASD may be characterized by enhanced non-social neural processing mechanisms during early childhood.

4.1 Introduction

Autism is one of the most severe neurodevelopmental disorders, with an increasing prevalence over the past two decades (60 in 10000), and is characterised by a "triad of impairments" in communication, social interaction, and restricted interests and repetitive behaviours (American Psychiatric Association, 2000; Levy, Mandell & Schultz, 2009). According to the recently published Diagnostic Statistical Manual of Mental Disorders-fifth edition (DSM-V; American Psychiatric Association, 2013), autism, termed as *Autism Spectrum Disorder,* is now considered a single diagnostic umbrella, including all subtypes of autism, previously termed as *Pervasive Developmental Disorders,* including *Autistic disorder, Asperger's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS;* American Psychiatric Association, 2000). Autism Spectrum Disorder (ASD) is still characterised by symptoms of severe deficits in communication and social interaction, as well as repetitive behaviours or restricted interests in particular subjects, which fall on a continuum or spectrum, varying from mild to severe from person to person (American Psychiatric Association, 2013).

Qualitative impairments in communication and social interaction in ASD include difficulties in the understanding and production of non-verbal behaviours, including facial expressions and gestures (American Psychiatric Association, 2000). Previous experimental studies have revealed behavioural difficulties in the comprehension and imitation of other people's actions and gestures in both children and adolescents with ASD (e.g. Cossu et al., 2012; Ingersoll, 2008a; Mundy et al., 1986; Rogers et al., 1996; Vanvuchelen, Roeyers & de Weerdt, 2010), which have also been found to be correlated with expressive language skills in young children with autism (e.g. Stone et

al., 1997). In addition, recent studies examining the perception of goal-directed actions have reported difficulties in interpreting social cues, such as pointing gestures, in order to understand other people's actions and intentions in children with autism (e.g. Falck-Ytter et al., 2012; Vivanti et al., 2011). Similarly, previous research employing Point-Light Displays (PLDs) presenting biological motion (Johansson, 1973) has revealed impairments in the detection and recognition of biological motion in both children and adults with autism (e.g. Atkinson, 2009; Blake et al., 2003; Cook et al., 2009; Freitag et al., 2008; Koldewyn et al., 2010; Nackaerts et al., 2012; Swettenham et al., 2013).

In order to better understand the neural underpinnings of atypical perception of human actions and biological motion in ASD, several research groups have utilised neuroimaging and electrophysiological research techniques. Functional magnetic resonance imaging (fMRI) studies of biological motion have revealed reduced activation of brain networks associated with biological motion processing, including the superior temporal sulcus (STS) and the inferior parietal lobule (IPL), in children and adults with ASD, as well as impaired functional connectivity between the STS and the temporoparietal junction in adults with ASD (e.g. Castelli et al., 2002; Freitag et al., 2008; Herrington et al., 2007; Kaiser et al., 2010; Koldewyn, Whitney & Rivera, 2011; McKay et al., 2012). Notably, Koldewyn, Whitney, and Rivera (2011) showed that neural processing of non-biological coherent motion was not deficient in adolescents with ASD, providing additional evidence that neural processing deficits may be specific to biological motion (see also Vandenbroucke et al., 2008; White et al., 2006). An impaired biological motion processing mechanism in autism was also revealed by an event-related potentials (ERP) study, providing higher temporal resolution and, therefore, more information about the roles of early sensory and later cognitive stages of

processing of biological motion (Kroger et al., 2013). More specifically, Kroger et al. (2013) reported reduced and atypically lateralised early sensory responses, as well as reduced activity over central-parietal channels at a later stage of perceptual processing (P400) in children and adolescents diagnosed with ASD.

Along with previous research investigating biological motion processing in autism, several research groups have also investigated the perceptual processing of human actions in individuals with ASD by examining activity associated with functioning of the mirror neuron system (MNS; Rizzolatti et al., 2001). The MNS is a specialized neural mechanism that has been primarily thought to underlie the perceptual processing of others' actions (see also *Chapter 1, section 1.1.3.1*; Rizzolatti et al., 2001). Mirror neuron activity in the frontoparietal network is thought to be reflected in electroencephalography (EEG) oscillations in the 8-13 Hz mu frequency band recorded from electrodes over primary motor cortex (Pineda, 2005). The mu rhythm is a resting state EEG rhythm, which has been found to be 'suppressed' in humans, when mirror neurons fire asynchronously during both the execution and observation of human actions (e.g. moving hand), relative to non-human actions (e.g. moving object; Pineda, 2005). Previous EEG studies in autism have reported a lack of mu rhythm (8-13 Hz) suppression, recorded from central channels, during the observation of hand actions (e.g., moving hand or gripping action) in both children and adults with ASD (e.g., Bernier et al., 2007; Oberman et al., 2005; but see also Fan et al., 2010; Raeymaekers, Wiersema & Roeyers, 2009). Similar impairments in the mirror neuron network in individuals with ASD have also been observed in other studies using different methodologies, including magnetoencephalography (MEG; Honaga et al., 2010), fMRI (e.g. Bastiaansen et al., 2011; Dapretto et al., 2005; Martineau et al., 2010),

electromyography (EMG; Cattaneo et al., 2007) and transcranial magnetic stimulation (TMS; Enticott et al. 2012; Theoret et al., 2005; see also, Hamilton, 2013, for a review). Interestingly, though, in an EEG study, Oberman, Ramachandran and Pineda (2008) found that mu rhythm was attenuated during the observation of hand actions in children with ASD, but only when the person performing the action was familiar to them.

The aforementioned findings by Oberman, Ramachandran, and Pineda (2008) might be associated with Dawson and colleagues' (2012) hypothesis that social and language impairment in autism might be driven by reduced attention to social cues, such as faces or other people's actions and gestures. In fact, several behavioural research studies have reported that children and adolescents with ASD pay less attention to visual or auditory social cues, including others' actions and speech sounds (e.g. Dawson et al., 1998; Klin, 1991; Klin et al., 2002b; Shultz, Klin & Jones, 2011), and sometimes show a stronger preference for non-social stimuli, such as geometric patterns or non-speech analogues, compared to controls (e.g. Klin et al., 2009; Kuhl et al. 2005; Pierce et al., 2011). Reduced social attention and experience with social interactions may be related to differential or reduced neural responses in children with ASD, possibly driven by previous social experiences and familiarity (see also Hamilton, 2013). More specifically, according to Dawson's (2008) *Social Motivation Hypothesis*, impaired neural systems associated with reward processing may underlie deficient social attention mechanisms in ASD, which may then lead to reduced social engagement and experience of the social world, as well as reduced cortical specialization and impaired function of brain mechanisms underlying social cognitive processing (Abrams et al., 2013; see also, Nelson, 2001).

Dawson's (2008) hypothesis has received support from recent findings revealing that brain areas, such as the STS, involved in the neural processing of auditory social stimuli, including human voice and speech, have been found to be underconnected with other brain structures associated with social reward processing in children with ASD (Abrams et al., 2013). Interestingly, several electrophysiological studies have reported atypical processing of speech in individuals with ASD (Ceponiene et al., 2003; Coffey-Corina, Padden, & Kuhl, 2008; Kuhl et al., 2005; Lepisto et al., 2005; Lepisto et al., 2007; Lepisto et al., 2006; Whitehouse & Bishop, 2008). For example, previous studies employing ERP oddball paradigms (presenting streams of standard speech sounds versus rare "oddball" stimuli) have revealed slightly smaller P1 responses (Ceponiene et al., 2003), and smaller MMN, P3 and N4 responses to speech and non-speech sounds (e.g. Ceponiene et al., 2003; Kuhl et al., 2005; Lepisto et al., 2005; Lepisto et al., 2006) in children with ASD. Most relevant to the current study and based on previous findings revealing the development of specialized human voice processing mechanisms in the temporal cortex, by 7 months of age (Grossman et al., 2010; Lloyd-Fox et al., 2012), a recent functional near-infrared spectroscopy (fNIRS) study conducted by Lloyd-Fox and colleagues (2013) examined the perceptual processing of human voices in 4- to 6-month old siblings of children diagnosed with autism, who were at higher risk of developing the disorder (see also Constantino et al., 2010; Ozonoff et al., 2011). More specifically, the authors used social acoustic stimuli produced by non-speech adult vocalizations (laughing, crying, yawning, coughing), and non-social acoustic stimuli produced by environmental or object sounds (rattles, squeaky toys, running water), and found that the high-risk group exhibited reduced haemodynamic responses during the

social-vocal condition compared to low-risk controls. However, no significant group differences were found for the non-vocal condition (Lloyd-Fox et al., 2013).

Although there is extensive evidence for atypical perceptual processing of both visual and auditory social stimuli, such as human actions and speech, in children with ASD, little is known about how they process non-vocal auditory stimuli produced by human movement and actions (e.g., hand clapping, hands ripping paper). Numerous EEG and fMRI studies have shown that a common neural network, including frontoparietal and temporal areas, is activated in response to both visual and auditory action-related cues in neurotypical adults (e.g. Aglioti & Pazzaglia, 2010; Bidet-Caulet et al., 2005; Giusti et al., 2010; Kaplan & Iacoboni, 2007; Pizzamiglio et al., 2005; Ricciardi et al., 2009). Based on previous visuo-auditory and auditory-auditory repetition suppression (RS) ERP paradigms employed by Pizzamiglio et al. (2005) and Giusti et al. (2010) in adults (see also, *Chapter 1, Section 1.1.3.4 & Chapter 3, Section 3.1*), as well as our previous findings in typically developing children (see *Chapter 3*), in the present study, we used an auditory-auditory, RS ERP paradigm, in order to investigate the nature and the time-course of human action-related and non-human action-related sound processing in 4- to 6-year old, high-functioning children with ASD, when compared with typically developing children matched for gender, chronological age, and verbal ability. Repetition suppression is a commonly used experimental method allowing for the examination of neuronal adaptation and "predictive coding" of repeated versus non-repeated stimuli, which reflects habituation and familiarity with the stimulus properties, as part of a perceptual learning process (Baldeweg, 2006; Turk-Browne, Scholl & Chun, 2008) (see also, *Chapter 2, Section 2.2*). In addition, we explored the relationship between perceptual processing of human

and non-human action sounds and verbal and non-verbal ability, as well as social and communication skills in both the ASD and control groups.

The investigation of the neural mechanisms underlying auditory perceptual processing of other people's actions in children with ASD will extend a previous line of research revealing impairments in visual processing of human actions and biological motion (e.g. Bernier et al., 2007; Kroger et al., 2013; Oberman et al., 2005), as well as in speech and human voice processing in autism (e.g. Abrams et al., 2013; Ceponiene et al., 2003; Eyler, Pierce, & Courchesne, 2012; Lloyd-Fox et al., 2013). Moreover, the current study will enrich our knowledge of the potential neural bases of the communication and social interaction difficulties experienced by children with autism.

Aims of the study

The aims of the present study were:

a) to examine whether children with ASD exhibit repetition suppression effects in response to human and non-human action sounds, by showing differential responses to repeated versus non-repeated stimuli,
b) to investigate the neural time-course of human action sound processing in children with ASD, and whether neural responses to human action sounds are delayed, reduced or increased in children with ASD, when compared with typically developing children,
c) to investigate whether intact or enhanced neural responses are elicited by non-human-action sounds in the ASD group relative to controls,
d) to determine whether there are any lateralization differences for human or non-human action sound processing between the groups,

e) to examine the relationship between perceptual processing of action- and non-action-related sounds and language ability, nonverbal ability, social and communication skills, and ASD behavioural symptoms, as measured by the Autism Diagnostic Observation Schedule (ADOS).

4.2 Method

4.2.1 Sample

Participants were recruited from the Birmingham, West Midlands, region of the United Kingdom, through the distribution of research subject recruitment flyers that have been specifically approved by the University of Birmingham Internal Review Board (IRB), and visits at local parent support groups for parents of toddlers and young children with ASD and local schools for children with special needs. In addition, some families were recruited through the "Peach" network for children with autism in Berkshire, and the British Autism Study of Infant Siblings (BASIS) network in London, United Kingdom. Parents, who provided their contact details to the researchers of the Autism Research Group at the University of Birmingham, were contacted in order to be informed about studies that would be appropriate for their child's age and developmental level.

As long as parents verbally agreed for their child to take part in the current study, they visited the Infant and Child Lab at the University of Birmingham, where they were asked to read and sign a University of Birmingham Internal Review Board (IRB) approved consent form to approve their child's participation in the study (see *Appendices A2, A3*). Parents were also asked to complete a brief questionnaire and

provide information about any medical complications during pregnancy or birth, issues related to their child's course of physical and neurological development, and/or any medication that was administered to their child (see *Appendices B1, B2*). Children who had experienced neurological problems, such as epilepsy, were excluded from participation in this study. Health-related problems that are not thought to affect a child's brain development, such as allergies, were not considered grounds for dismissal. Bilingual children were also excluded from participation.

Twenty-three children with autism spectrum disorders (ASD; 22 males, 1 female) and twenty typically developing children (TD; 18 males, 3 females), aged 4- to 6-years, participated in the study. Five children with ASD (all males) were excluded from the analyses due to low verbal ability, and two typically developing children (1 male, 1 female) were excluded due to motor and ocular motor artifacts in the ERP data. Therefore, the current analyses are based on ERP data from 18 children with ASD (17 males, 1 female) and 18 typically developing children (17 males, 1 female), individually matched for gender, chronological age (CA), and verbal age (VA). The mean chronological age of the final sample of children with ASD (M=62.8 months, *S.E.* = 2.17) was not significantly different from the mean chronological age of the TD group (M=60.3 months, *S.E.*= 2.42), t (34)=0.77, p> 0.05, equal variances assumed. None of the children taking part in this study had a history of seizures or any other neurological disorder, and all participants had normal, or corrected to normal, hearing (two children with ASD had a history of a Glue ear at an earlier age). In addition, three children in the ASD group were on melatonin at the time of the study. All participants were right handed, apart from three children in the ASD group and four children in the TD group, who were left handed (see *Table 4,* for group characteristics).

4.2.2 Behavioural measures

4.2.2.1 Autism Diagnostic Observation Schedule-Generic (ADOS-G)

The Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord et al., 2000), which is considered the "gold standard" semi-structured clinical assessment for toddlers, children, and adults with autism spectrum disorders, was used for the behavioural characterization of children with a community diagnosis of an ASD, as well as children awaiting a formal community diagnosis. Although the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter & Le Couteur, 1994) provides a detailed developmental history for children on the autism spectrum and diagnostic specificity has been found to improve when both measures are used (Kim & Lord, 2012), its use in this study was not possible due to time limitations. However, the ADOS-G combined with the Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003), a second-level screening questionnaire used here, or the use of the ADOS-G alone, has been found to have a higher predictive value, when compared with the combination of the ADOS-G and ADI-R in a large sample of 20- to 40-month old children at high risk for ASD (Osterling et al., 2010).

Eleven children in the ASD group had a community diagnosis of an autism spectrum disorder and another seven children were awaiting a formal clinical diagnosis, which was verified through the administration of the ADOS-G in the Infant and Child Lab by a trained researcher. From the group of children with a formal clinical diagnosis, 7 children had a diagnosis of Autistic Disorder, 3 children were diagnosed with Asperger's Disorder, and 1 child received a diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified (PDD–NOS). Only one 5-year old child, diagnosed with Asperger's Disorder at 3 years of age, did not meet the criteria for an autism

spectrum disorder on the ADOS-G (total score=6, ADOS cut-off=7), although he met the cut-off scores on the communication and social interaction subscales. All children awaiting a formal community diagnosis met the criteria for autism (*n*=2) or autism spectrum disorder (*n*=5) on the ADOS-G.

Overall, based either on the clinical diagnoses or on the results of the ADOS assessments, all children in the ASD group met the diagnostic criteria for an autism spectrum disorder. More specifically, 9 of the 18 children met the diagnostic criteria for Autistic Disorder, 3 met the criteria for Asperger's Disorder, and the remaining 6 met criteria for Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS) (see *Table 4* for mean ADOS scores).

4.2.2.2 Social Communication Questionnaire (SCQ)

The Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003; see also *Appendix B3*) is a second-level screening questionnaire for children with ASD, and was completed by parents of all participants, in order to screen for social and communication difficulties in both groups. In addition, the relationship between brain activity, elicited by human-action sounds, and social and communication skills was also examined in both groups. Only one family from the ASD group did not complete the SCQ. No children in the typical group received a score higher than 12, whereas all children in the ASD group, but two, received a score of 16 or higher, revealing autism symptomatology. The SCQ scores in the ASD group (M=23.9, $S.E.$=1.98) were significantly higher that those in the TD group (M=4.3, $S.E.$=0.8), $t(21)=9.22$, $p<0.01$, equal variances not assumed (see *Table 4*).

4.2.2.3 Language and cognitive assessments

The standardized cognitive measures used for the assessment of verbal and non-verbal ability in the current study were the Mullen Scales of Early Learning (MSEL; Mullen, 1995) and the British Ability Scales (BAS; Elliott, Smith & McCulloch, 1997). The MSEL was used for the assessment of verbal and non-verbal ability of 4- and 5-year old children in the ASD and typical groups, whereas the BAS was used for the assessment of verbal and non-verbal ability of old 5-year old and 6-year old participants in both groups. Previous findings showing good convergent validity of the MSEL and the Differential Ability Scales (DAS; Elliott, 1990, 2007) allowed the authors of the current study to use the MSEL along with the BAS, which is the original, British version of the DAS (Bishop, Guthrie, Coffing, & Lord, 2011). Verbal ability measures were also used in order to individually match children in the ASD and typical groups. In addition, both verbal and non-verbal ability measures were used in order to investigate the relationship between brain activity associated with human action sound processing and verbal and non-verbal skills.

Although the difference in verbal age-equivalent scores between the chronological age matched groups (ASD: M=53.8 months, $S.E.$=3.62; TD: M=61.4 months, $S.E.$=3.18) was not statistically significant ($t(34)$=-1.57 , p<0.05, equal variances assumed), they were not individually matched for verbal ability and the verbal age range in the ASD group was larger than that one of the typical group (see *Table 4*). Therefore, an additional set of analyses was undertaken including only 14 children of the initial ASD group, individually matched for verbal age with 14 TD controls. Eleven children within each group completed the MSEL, whereas 3 children in each group completed the BAS. Four children, who had lower verbal ages and had to be matched

with younger typically developing toddlers, were excluded from the ASD group. This choice was based on previous claims highlighting the importance of life experience for the perceptual processing of social stimuli, such as faces, which has been suggested to be functioning independently (Karmiloff-Smith et al., 2004). This additional analysis was based on two groups of children with ASD and typically developing children, equated for life experience with human actions to the best possible extent, as both groups were within the same chronological age range and individually matched for verbal age. No significant differences for verbal age were found between the ASD (*M*=58.3 months, *S.E.*=3.82) and the TD group (*M*=59 months, *S.E.*=3.67), *t*(26)=-0.14, *p*>0.05, equal variances assumed. Table 5 shows the characteristics of the participants included in the additional set of analyses in the ASD (n=14) and the TD groups (n=14), as well as the significance levels from the statistical comparisons between the groups. Significance levels did not change for group differences in SCQ scores (ASD: M=23.5, S.E.=2.37; TD: M=4.4, S.E.=0.92), t(16)=7.49, p<0.01, equal variances not assumed. Interestingly, although participants were not individually matched for non-verbal age in either comparison, in this second set of analyses, there were no significant non-verbal age differences between the ASD (M=58.6, S.E.=2.38) and the TD group (M=65.1, S.E.=4.21), t(26)=-1.35, p>0.05, equal variances assumed.

Characteristics	ASD (*n*=18)	TD (*n*=18)	Group comparison (P-value)
Gender	17 males, 1 female	17 males, 1 female	N/A
Handedness	15 right 3 left	14 right 4 left	N/A
Chronological age (months)	62.8 (9.2) range: 50 - 80	60.3 (10.3) range: 47 - 79	0.45
MSEL - BAS Verbal age (months)	53.8 (15.4) range: 32.5 - 94	61.4 (13.5) range: 41 - 93.5	0.13
MSEL - BAS Non-Verbal age (months)	56.6 (10.6) range: 30.5 - 77.5	66 (14.8) range: 45 - 96	0.04
SCQ	*n=17* 23.9 (8.1) range: 5 – 34	4.3 (3.4) range: 0 - 12	0.00
ADOS- Communication subscale	4.3 (1.6)	N/A	N/A
ADOS- Social subscale	7.2 (2.4)	N/A	N/A
ADOS- Total score	11.4 (3.8)	N/A	N/A

Table 4*. Characteristics of ASD and TD control groups, individually matched for chronological age - Means (S.D.) and results of group comparisons, based on independent samples t-tests.*

Characteristics	ASD (*n*=14)	TD (*n*=14)	Group comparison (P-value)
Gender	13 males, 1 female	13 males, 1 female	N/A
Handedness	12 right 2 left	11 right 3 left	N/A
Chronological age (months)	64.5 (8.5) range: 54 - 80	59.6 (10.9) range: 47 - 79	0.19
MSEL - BAS Verbal age (months)	58.3 (14.3) range: 40 - 94	59 (13.7) range: 41 - 93.5	0.89
MSEL - BAS Non-Verbal age (months)	58.6 (8.9) range: 47.5 - 77.5	65.1 (15.7) range: 45 - 96	0.19
SCQ	*n=17* 23.5 (8.6)	4.4 (3.4)	0.00
ADOS- Communication subscale	3.7 (1.1)	N/A	N/A
ADOS- Social subscale	6.3 (1.8)	N/A	N/A
ADOS- Total score	10 (2.7)	N/A	N/A

Table 5. *Characteristics of ASD and TD control groups, individually matched for verbal age - Means (S.D.) and results of group comparisons, based on independent samples t-tests.*

4.2.3 Stimuli- Experimental procedure

The ERP assessment utilised in the present study was based on a novel auditory-auditory repetition suppression ERP paradigm that included a single block of approximately 570 trials, lasting for 30 minutes and presenting two types of sounds: human action (e.g. hands clapping, hands ripping paper) and non-human action (helicopter blades spinning, ocean waves) -related sounds. Each type of sound was followed by a sound from either the same or the other perceptual category, resulting in four trial types: a) congruent (repeated) human action-related sound trial, b) incongruent (non-repeated) human action-related sound trial, c) congruent (repeated) non-human action-related sound trial, and d) incongruent (non-repeated) non-human action-related sound trial (see also *Chapter 2, Sections 2.3, 2.4*).

4.2.4 ERP Recording and Analysis

Brain electrical activity was recorded continuously using a child-friendly, high-density, 128-channel Hydrocel Geodesic Sensor Net (HCGSN, Electrical Geodesics Inc., Eugene, Oregon) (Tucker, 1993). EEG was referenced to a single vertex electrode, Cz (sample rate = 500 Hz). All bioelectrical signals were recorded using EGI NetStation amplifiers with an input impedance of less than 100 kΩ.

EEG data were band-pass filtered offline at 0.1 to 40 Hz and segmented to epochs, using NetStation 4.2 software (Electrical Geodesics). Epochs were time-locked to the second auditory stimulus in the trial, contained 100 ms pre-stimulus time and 700 ms post-stimulus time, and were organised by stimulus type [human action sound repetition (congruent), human action sound non-repetition (incongruent), non-human action sound repetition (congruent), non-human action sound non-repetition

(incongruent)]. Data were then processed using an artifact-detection tool, which marked channels bad, if the recording was poor for greater than 99 % of the time (threshold maximum-minimum, >150), and segments if they contained more than 12 bad channels, eye-blinks or eye-movements. Following this automated artifact detection process, individual examination of each of the trials by a trained EEG researcher was also performed in order to remove trials including any remaining ocular or motor artifacts from the data. All children produced a minimum of 40 viable ERP trials per experimental condition, apart from one typically developing child who had 30 to 43 artifact-free trials per condition, and was included in both analyses. Tables 6 and 7 show the means of motor and ocular-motor artifact-free trials per condition, per group, for both analyses. Planned contrasts revealed that the numbers of artifact-free trials per condition were not significantly different between the groups (see *Tables 6, 7*, for significance levels). In addition, for artifact-free trials containing 12 or fewer bad channels, data in those channels were replaced using a spherical spline interpolation algorithm (Srinivasan et al., 1996). Finally, individual subject data were averaged, re-referenced to an average reference, and baseline-corrected to a 100 ms pre-stimulus interval.

Condition	ASD (*n*=18)	TD (*n*=18)	Group comparison (*P*-value)
Human action sounds			
Congruent	60.4 (21.2)	69.6 (18.2)	0.17
Incongruent	63.3 (21.9)	68.6 (19.3)	0.44
Non-Human action sounds			
Congruent	64.2 (19.5)	71.5 (17.1)	0.24
Incongruent	61.9 (19.8)	68.8 (19)	0.3

Table 6. *Descriptive data - Means (S.D.) of artifact-free trials per condition in chronological age (CA)-matched ASD and TD groups, and the results of group comparisons, based on independent samples t-tests.*

Condition	ASD (*n*=14)	TD (*n*=14)	Group comparison (*P*-value)
Human action sounds			
Congruent	64.1 (22.6)	67.1 (18.9)	0.71
Incongruent	65.9 (24.1)	66.7 (19.9)	0.92
Non-Human action sounds			
Congruent	66.8 (20.9)	69.5 (17.2)	0.71
Incongruent	63.3 (22.2)	67.4 (18.6)	0.6

Table 7. *Descriptive data - Means (S.D.) of artifact-free trials per condition in verbal age (VA)-matched ASD and TD groups, and the results of group comparisons, based on independent samples t-tests.*

Electrode locations and time windows for analysis in the current study were selected based on ERP findings of the typical development study described in Chapter 3, on previous speech processing findings of ERP studies using oddball paradigms in individuals with ASD (e.g. Ceponiene et al., 2003; Kuhl et al., 2005; Lepisto et al., 2005; Lepisto et al., 2006), and on visual inspection of grand average ERP data, prior to any statistical analysis. Electrode sites that were selected for analysis included 33 frontal and frontocentral (11 left, 11 middle, 11 right), 14 temporal (7 left, 7 right), and 18 parietal (6 left, 6 middle, 6 right) electrodes (see *Figure 12*). Averaged ERPs obtained during all experimental conditions were analysed sample by sample in the 40-700 ms temporal window by using repeated-measures Analysis of Variance (ANOVA) and paired contrasts using bonferroni correction, in order to identify similarities or differences in repetition suppression effects in response to human action- versus non-human action-related sounds between the ASD and TD groups. Different time windows for human and non-human action sound processing over frontal, temporal and parietal electrode sites were selected for analysis. A comparison of the mean amplitude of the major ERP components between conditions and groups was conducted. In addition, the peak latency of some of the components was also analysed, in order to examine timing processing differences between children with ASD and chronological and verbal age matched controls.

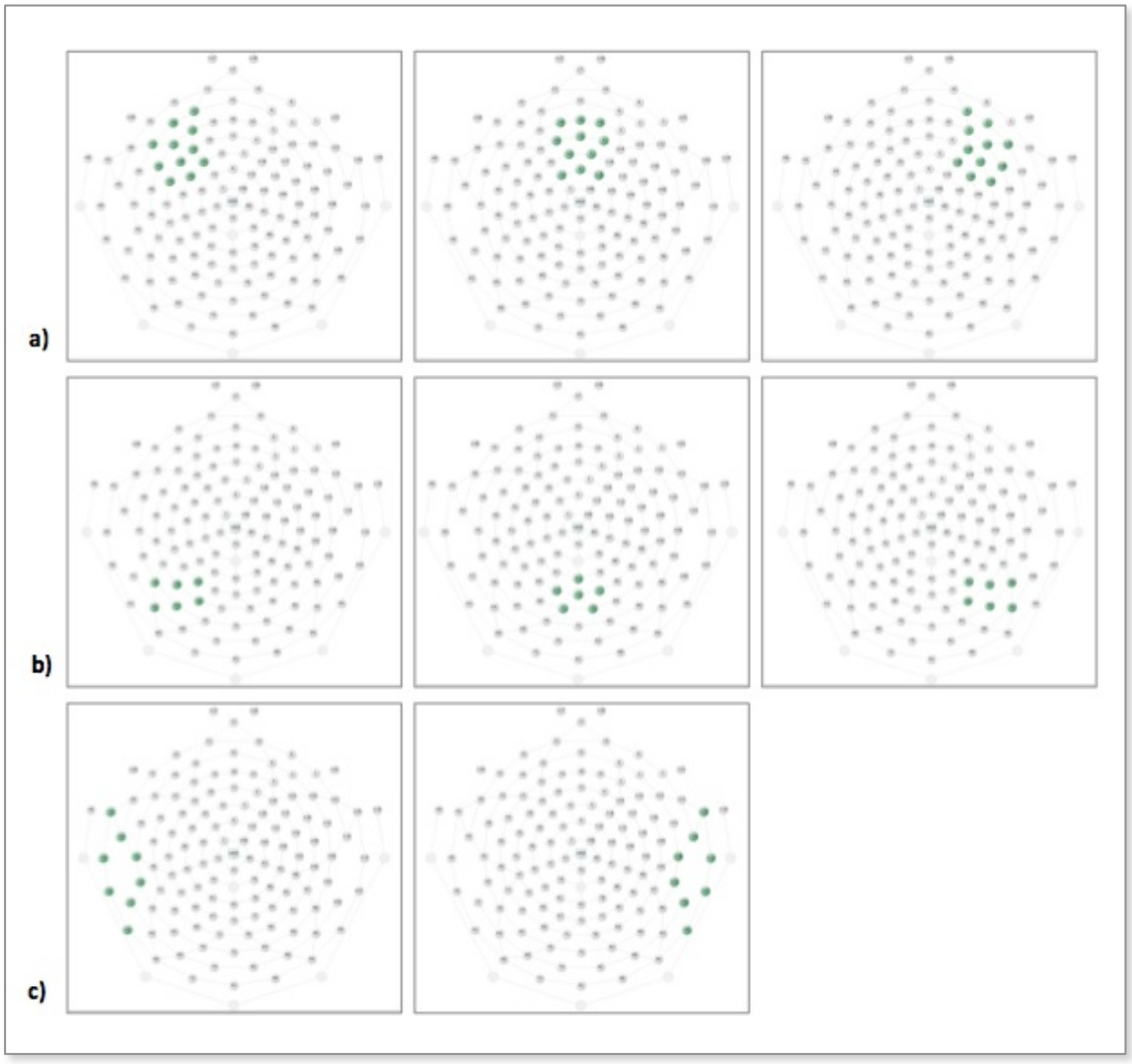

Figure 12. *Montage selected for analysis in the ASD and control groups.*

a) Left, middle and right frontal electrodes selected for the ERP data analyses. b) Left, middle and right parietal electrodes selected for the ERP data analyses, and c) Left and right temporal electrodes selected for the ERP data analyses.

4.3. Results

ERPs to human action sounds included two early sensory processing components (P1, N1), an early component reflecting stimulus feature mismatch cortical responses (P2), and two later perceptual processing components (N4, N600). ERPs to non-human action sounds included the P1 and N1 components for both groups and a later

component reflecting stimulus categorization (N2b). P1 and N1 (40-180ms) peaked at approximately 110 ms over the frontal and temporoparietal channels respectively, whereas P2 was identified within the time window 180-300 ms over the frontal cortex. In addition, N2b component (280-360 ms) was identified over the parietal sites only in the ASD groups, and N4 was identified within the time windows 360-500ms and 340-380ms over the frontal and parietal sites, respectively. Finally, N600 (540-660ms) was identified over the frontal region in both groups. Mean amplitude analysis was carried out on all ERP components, whereas peak latency analysis was carried out only on P1, N1 and frontal N4.

A between-subjects, repeated-measures ANOVA with stimulus type (human action sound, non-human action sound), condition (congruent / repeated stimuli, incongruent / non-repeated stimuli) and hemisphere (left, middle, right) as within-subjects factors, and group (ASD, CA- or VA-matched controls) as between-subjects factor, was carried out on the mean amplitude and peak latency of the selected components. However, only interactions between stimulus type and condition, revealing a significant repetition suppression effect, were considered for follow-up analyses, which included pairwise comparisons using Bonferroni correction, in order to explore ANOVA interactions further. In addition, the relationship between cortical responses to both human and non-human action sounds and chronological age, as well as cognitive and social communication skills in both groups was explored by conducting correlation analyses between the mean amplitude and peak latency of the selected components and chronological age in months, as well as scores achieved on the standardised behavioural measures and questionnaires employed in the current study. The latter included verbal and non-verbal age equivalents in months (as scored on the MSEL and BAS), the scores

on all the ADOS-G subscales (communication, reciprocal social interaction, imagination/creativity, stereotyped behaviours and restricted interests), the ADOS-G communication and social interaction total scores, and the SCQ scores. However, the results from these correlation analyses were viewed with caution due to the large number of factors included in the current analyses and the small sample recruited in the present study.

ERP waveforms presented in the next results sections reflect ERP data recorded from all children with ASD and typically developing controls that took part in the study, as the comparison of the ASD group with the chronological age (CA)- (n=18) and the verbal age (VA)-matched (n=14, 4 children of lower verbal age excluded) groups revealed the same results. The only difference between the results of the two analyses was found in the P1 and N1 peak latency over the frontal and temporal channels (see below).

Frontal activity

P1 (P110: 40-180ms)

A between-subjects, repeated-measures analysis of variance (ANOVA) with stimulus type (human action sound, non-human action sound), condition (congruent, incongruent) and hemisphere (left, middle, right) as within-subjects factors, and group (ASD, VA-matched controls) as between-subject factor was carried out on the P1 mean amplitude. The analysis revealed a significant interaction between stimulus type and condition, $F(1,26)=11.2$, $p<0.01$. Paired contrasts using Bonferroni correction showed that this interaction was driven by greater P1 responses to non-repeated (M=1.83μV, $S.E.$=0.3) relative to repeated (M=0.77μV, $S.E.$=0.23) non-human action sounds over the

frontal channels, $p<0.01$. These results were replicated by the comparison of the ASD and CA-matched groups, which also revealed a significant interaction between stimulus type and condition, $F(1,34)=14.31$, $p=0.001$ (see *Figure 13*). In addition, the investigation of the relationship between the P1 mean amplitude and social and communication skills revealed a significant positive correlation between the P1 amplitude in response to non-repeated non-human action sounds and ADOS communication scores in the ASD group (n=18), $r=.48$, $p<0.05$.

P1 peak latency analysis revealed no significant main effects or interactions for the comparison of the ASD and VA matched groups. However, a repeated-measures ANOVA with stimulus type (human action sound, non-human action sound), condition (congruent, incongruent) and hemisphere (left, middle, right) as within-subjects factors, and group (ASD, CA matched controls) as between-subject factor, revealed a significant interaction between stimulus and condition ($F(1,34)=5.15$, $p<0.05$), driven by faster P1 responses to repeated ($M=100.44$ms, $S.E.=3.26$) relative to non-repeated ($M=111.66$ms, $S.E.=3.16$) human action sounds (pairwise comparisons using Bonferroni correction: $p<0.01$) (see *Figure 14*). Correlation analyses also revealed a negative correlation between P1 peak latency in response to repeated human action sounds and non-verbal ability scores in the ASD group, $r=-.48$, $p<0.05$.

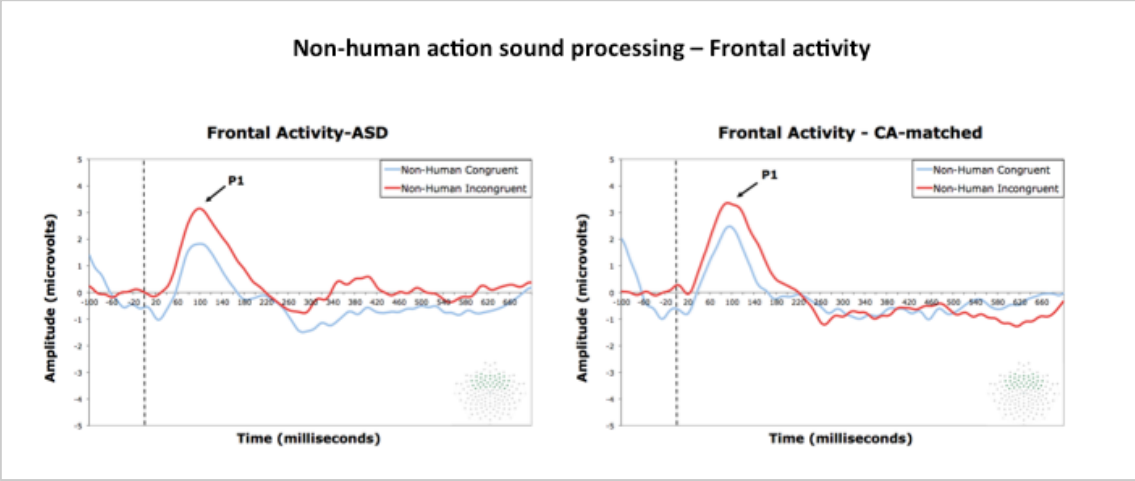

Figure 13. *Repetition suppression waveforms recorded over the frontal cortex for non-human action sounds in the ASD and CA-matched contol groups.*

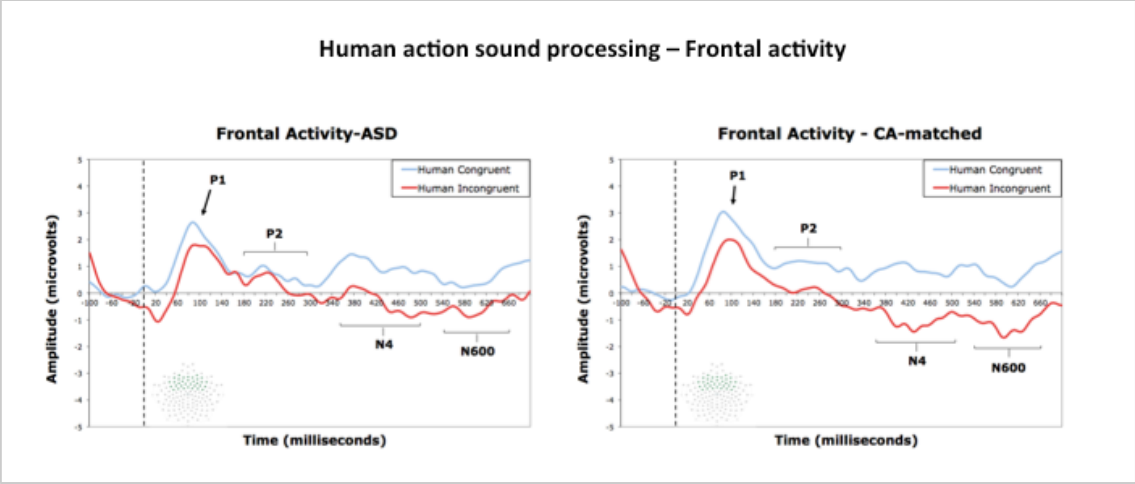

Figure 14. *Repetition suppression waveforms recorded over the frontal cortex for human action sounds in the ASD and CA-matched control groups.*

P2 (P240: 180-300ms)

Repeated-measures analyses of variance with stimulus type (human action sound, non-human action sound), condition (congruent, incongruent) and hemisphere (left, middle, right) as within-subjects factors, and group (ASD, VA/CA matched controls) as between-subject factor was carried out on the P2 mean amplitude and revealed a significant effect of stimulus type for both comparisons (ASD vs VA-matched controls:

$F(1,26)=7.26$, $p<0.05$; ASD vs CA-matched controls: $F(1,34)=9.23$, $p<0.01$) and a significant interaction between condition and group for the comparison of the ASD and VA-matched groups, $F(1,26)=9.06$, $p<0.01$ (see *Figure 14*). However, the interaction between stimulus type and condition was not significant for either comparison (ASD vs VA-matched controls: $F(1,26)=2.05$, $p=0.16$; ASD vs CA-matched controls: $F(1,34)=2.56$, $p=0.12$).

N4 (N430: 360-500ms)

A stimulus type (human action sound, non-human action sound), by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (ASD, VA-matched controls) repeated-measures ANOVA conducted on the N4 mean amplitude revealed a significant effect of stimulus type ($F(1,26)=4.68$, $p<0.05$), a significant effect of condition ($F(1,26)=6.51$, $p<0.05$), and a significant interaction between stimulus type and condition ($F(1,26)=9.96$, $p<0.01$). Paired contrasts using Bonferroni correction revealed that this effect was driven by a larger difference between N4 responses to non-repeated and repeated human action sound stimuli, $p<0.001$. Cortical responses to repeated human action sounds were more positive, whereas cortical responses to non-repeated human action sounds were negative. These results were replicated by the comparison of the ASD and CA-matched groups, which also revealed a significant effect of stimulus ($F(1,34)=4.02$, $p=0.05$), and a significant interaction between stimulus type and condition ($F(1,34)=15.21$, $p<0.001$) (see *Figure 14*). In addition, correlation analyses revealed that larger cortical responses to repeated human action sounds within the time window 360-500 ms were negatively associated with lower non-

verbal ability scores in the ASD group (n=18). However, this correlation was marginally significant, r=-.47, p=0.05.

N4 peak latency analysis on a slightly different time window (390-530 ms) after visual inspection of individual data revealed no significant effects or interactions.

N600 (540-670ms)

A stimulus type (human action sound, non-human action sound), by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (ASD, VA-matched controls) repeated-measures ANOVA conducted on the N600 amplitude revealed a significant effect of condition (F(1,26)=4.95, p<0.05), a significant interaction between condition and group (F(1,26)=8.17, p<0.01), and a marginally significant interaction between stimulus type and condition (F(1,26)=3.95, p=0.05). Paired contrasts using Bonferroni correction revealed that the latter was driven by a larger difference between N600 responses to non-repeated and repeated human action sound stimuli, p<0.05. These results were replicated by the comparison of the ASD and CA-matched groups, which also revealed a significant effect of condition (F(1,34)=4.4, p<0.05), and a significant interaction between stimulus type and condition (F(1,34)=7.05, p<0.05) (see *Figure 14*).

Temporal activity

N1 (N110: 40-180ms)

A repeated-measures ANOVA with stimulus type (human action sound, non-human action sound), condition (congruent, incongruent) and hemisphere (left, middle, right) as within-subjects factors, and group (ASD, VA matched controls) as between-

subject factor was carried out on the N1 mean amplitude and revealed a significant interaction between stimulus type and condition, $F(1,26)=6.57$, $p<0.05$. Paired contrasts using Bonferroni correction showed that this interaction was driven by greater N1 responses to non-repeated (M=-1.46μV, $S.E.$=0.17) relative to repeated (M=-0.74μV, $S.E.$=0.19) non-human action sounds over the temporal channels, $p<0.01$. These results were replicated by the comparison of the ASD and CA-matched groups, which revealed a significant effect of stimulus ($F(1,34)=6.22$, $p<0.05$) and a significant interaction between stimulus type and condition ($F(1,34)=7.59$, $p<0.01$) (see *Figure 15*). In addition, the investigation of the relationship between the N1 mean amplitude and social and communication skills revealed a significant negative correlation between the N1 amplitude in response to non-repeated non-human action sounds and ADOS communication scores in the ASD group (n=18), r=-.46, p=0.05.

In accordance with P1 peak latency analysis, a repeated-measures ANOVA conducted on the N1 peak latency for the comparison of the ASD and the CA-matched groups revealed a significant interaction between stimulus and condition ($F(1,34)=6.23$, $p<0.05$), driven by faster N1 responses to repeated (M=103.88ms, $S.E.$=2.68) relative to non-repeated (M=111.94ms, $S.E.$=3.43) human action sounds (pairwise comparisons using Bonferroni correction: $p<0.05$) (see *Figure 16*). However, peak latency analysis comparing the ASD and VA-matched groups revealed no significant effects or interactions.

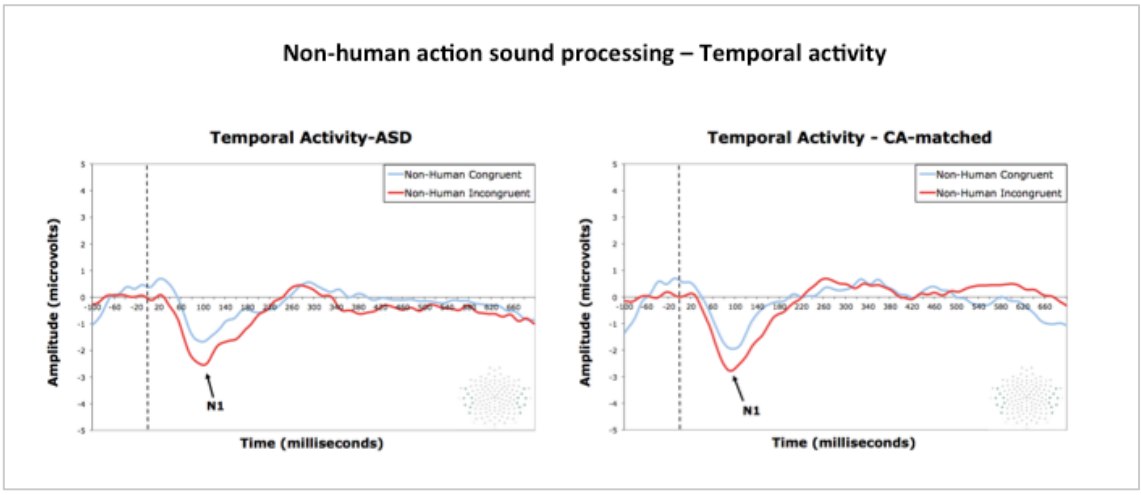

Figure 15. *Repetition suppression waveforms recorded over the temporal cortex for non-human action sounds in the ASD and CA-matched control groups.*

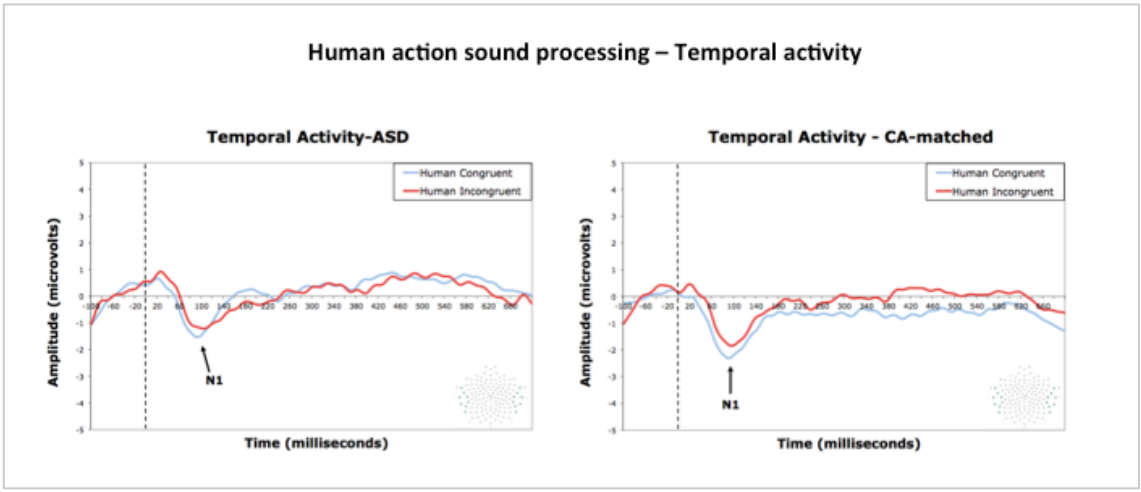

Figure 16. *Repetition suppression waveforms recorded over the temporal cortex for human action sounds in the ASD and CA-matched control groups.*

Parietal activity

N1 (N100: 40-180ms)

No significant main effects or interactions were revealed by repeated-measures analyses of variance carried out on the N1 mean amplitude or peak latency over the parietal cortex (see *Figures 17, 18*).

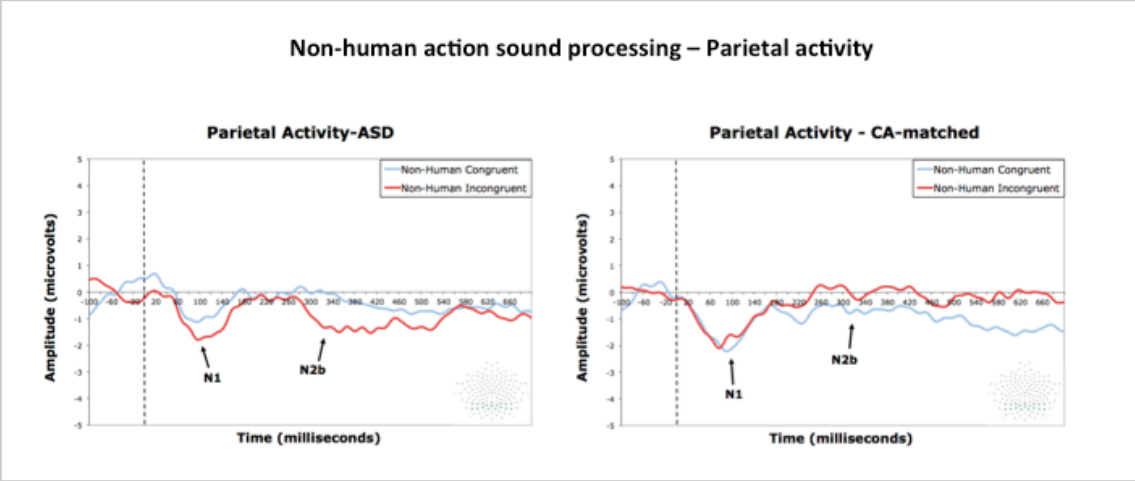

Figure 17. *Repetition suppression waveforms recorded over the parietal cortex for non-human action sounds in the ASD and CA-matched control groups.*

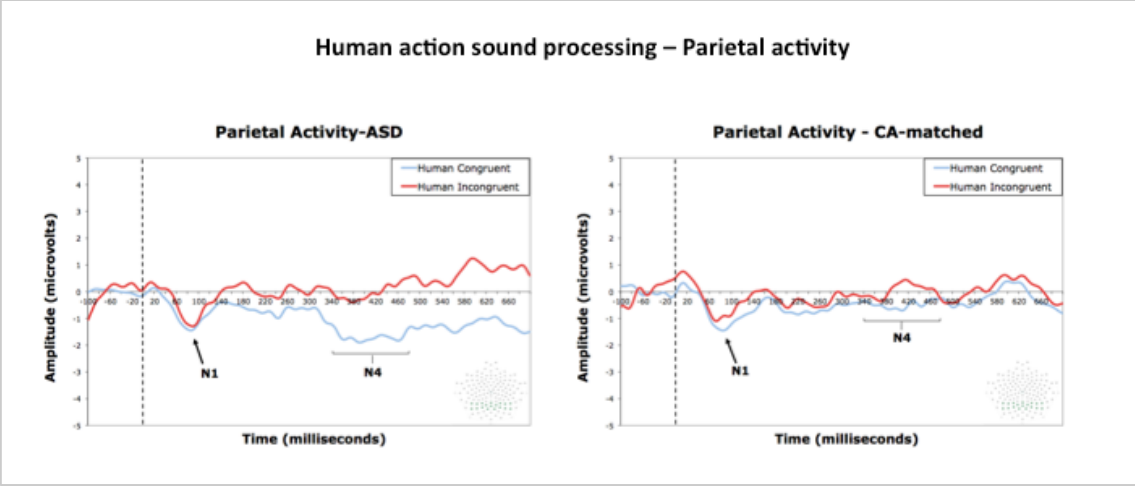

Figure 18. *Repetition suppression waveforms recorded over the parietal cortex for human action sounds in the ASD and CA-matched control groups.*

N2b (N320: 280-360ms)

A stimulus type (human action sound, non-human action sound), by condition (congruent, incongruent), by hemisphere (left, middle, right), by group (ASD, VA-matched controls) repeated-measures ANOVA conducted on the N2b mean amplitude revealed a significant effect of hemisphere ($F(2,52)=6$, $p<0.01$), a significant interaction between stimulus type and condition ($F(1,26)=4.99$, $p<0.05$), and a significant

interaction between stimulus type, condition and group ($F(1,26)=8.45$, $p<0.01$). Paired contrasts using Bonferroni correction revealed that this effect was driven by a larger N2b amplitude in response to non-repeated (M=-1.26μV, $S.E.$=0.64) relative to repeated (M=0.26μV, $S.E.$=0.73) non-human action sound stimuli in the ASD group, $p<0.05$. These results were replicated by the comparison of the ASD and CA-matched groups, which also revealed a significant effect of hemisphere ($F(2,68)=8.21$, $p=0.001$), and a significant interaction between stimulus type, condition and group ($F(1,34)=4.57$, $p<0.05$) (see *Figures 17, 19, 20*).

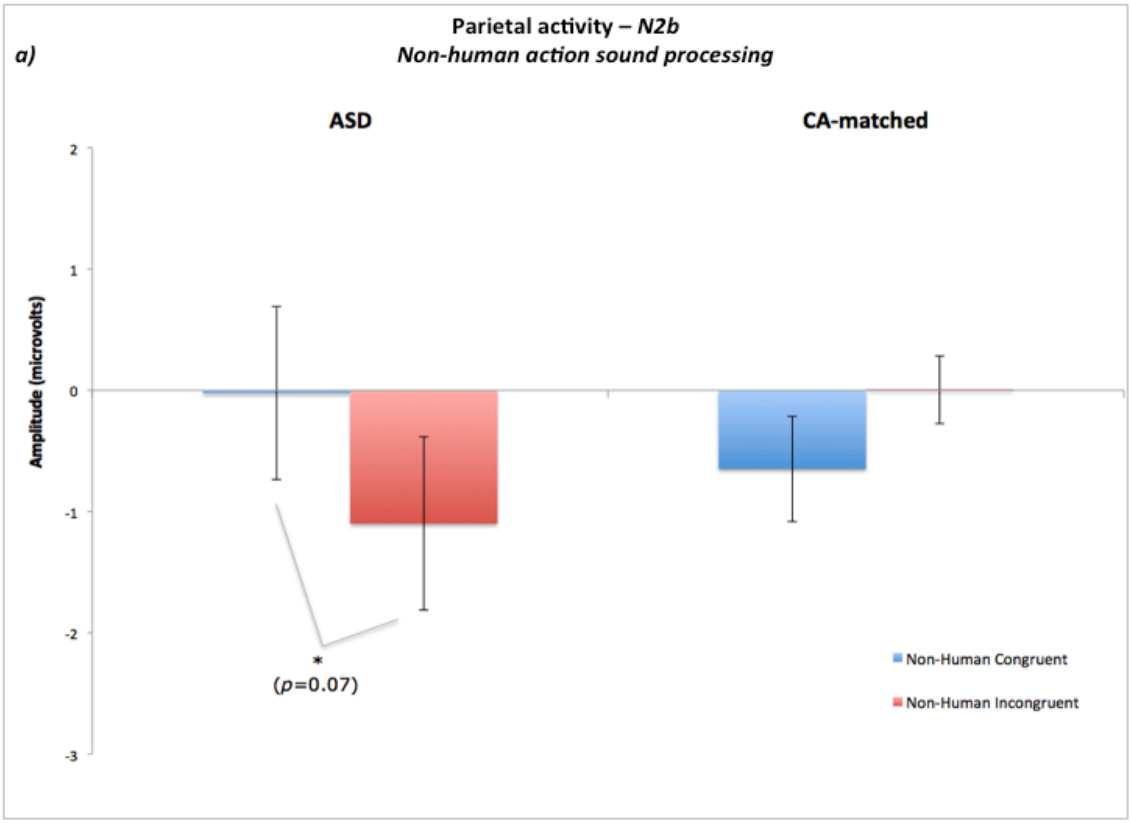

Figure 19. *N2b mean amplitude in response to repeated and non-repeated non-human action sounds over the parietal cortex in the ASD and CA-matched control groups.*

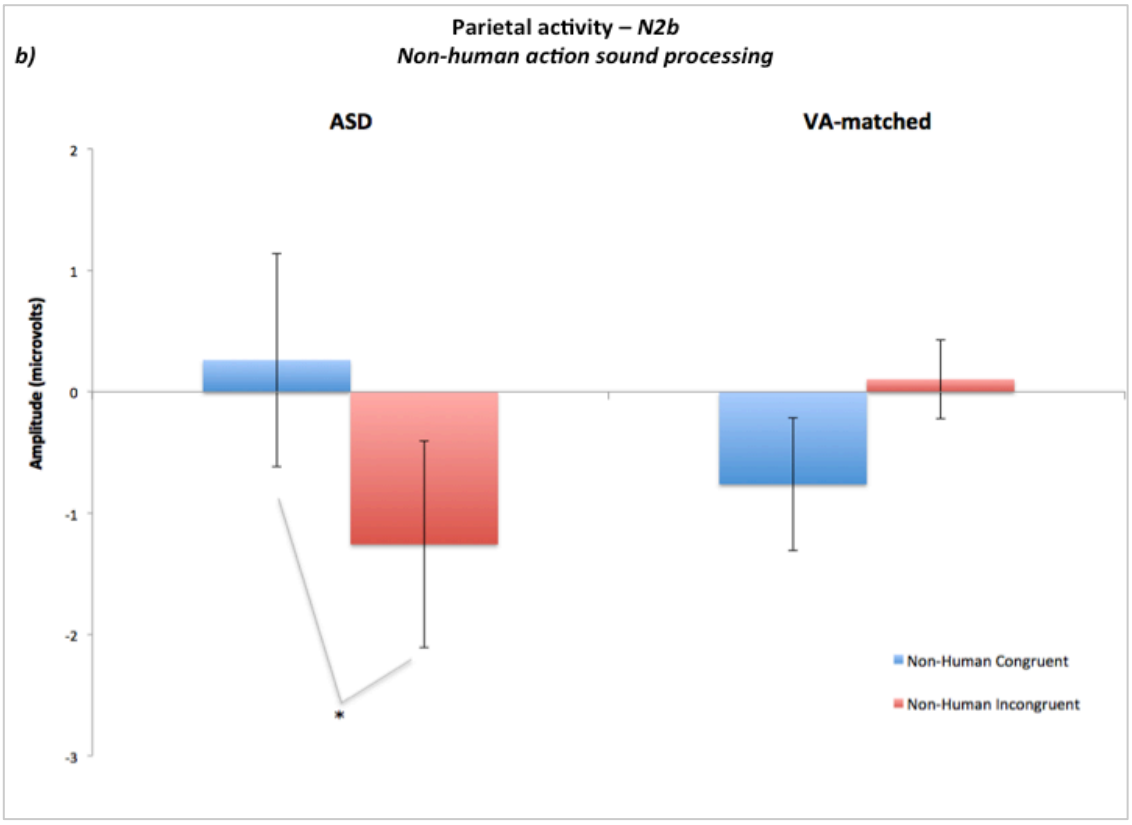

Figure 20. *N2b mean amplitude in response to repeated and non-repeated non-human action sounds over the parietal cortex in the ASD and VA-matched groups.*

N4 (N410: 340-480 ms)

A repeated-measures ANOVA with stimulus type (human action sound, non-human action sound), condition (congruent, incongruent) and hemisphere (left, middle, right) as within-subjects factors, and group (ASD, VA matched controls) as between-subject factor was carried out on the N4 mean amplitude and revealed a significant effect of hemisphere ($F(2,52)=4.98$, $p<0.05$), a significant interaction between stimulus type and condition ($F(1,26)=4.4$, $p<0.05$), and a significant interaction between stimulus type, condition and group ($F(1,26)=6.19$, $p<0.05$). Paired contrasts using Bonferroni correction showed that this interaction was driven by greater N4 responses to repeated (M=-1.96μV, $S.E.$=0.45) relative to non-repeated (M=0.16μV, $S.E.$=0.52) human action

sounds over the parietal channels in the ASD group, $p<0.05$. A significant interaction between stimulus type, condition and group was also revealed for the comparison of the ASD with the CA-matched groups, $F(1,34)=3.86$, $p=0.05$ (see *Figures 18, 21, 22*).

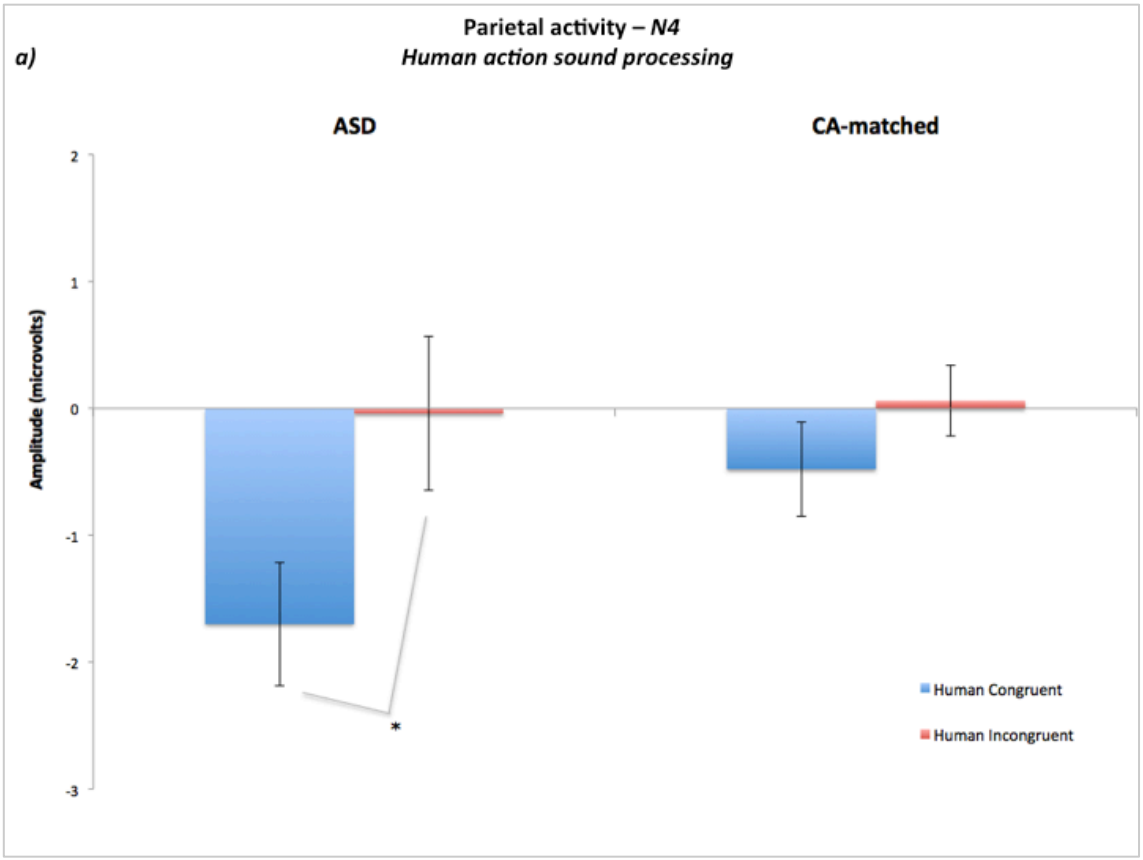

Figure 21. *N4 mean amplitude in response to repeated and non-repeated human action sounds over the parietal cortex in the ASD and CA-matched groups.*

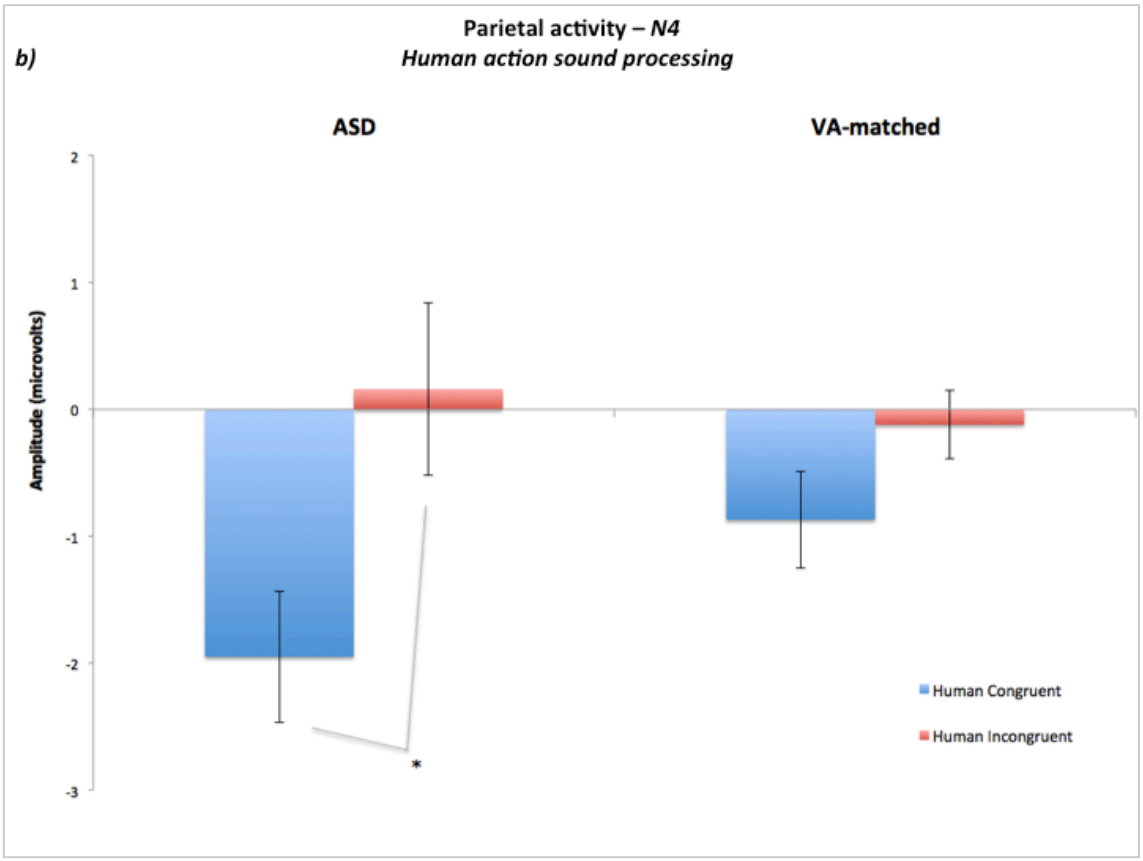

Figure 22. *N4 mean amplitude in response to repeated and non-repeated human action sounds over the parietal cortex in the ASD and VA-matched groups.*

4.4 Discussion

The aim of the current study was to investigate action-related sound processing in young children with autism and typically developing children, matched for gender, and chronological and verbal age. ERP responses to human action sounds included P1/N1, N4, and N600 components, whereas ERP waveforms to environmental or object sounds included P1/N1 and N2b components. No significant differences were found between the groups for early sensory processing (P1/N1) of either human or non-human action sounds over the frontal or temporal cortices. In addition, although no significant group differences were revealed for the N4 and N600 components over the frontal sites, the N4

amplitude in response to repeated human action sounds over the parietal channels was found to be significantly larger in the ASD group compared to controls. Similarly, within a slightly earlier time window, children with ASD exhibited greater N2b responses to non-repeated environmental or object sounds, when compared with the typically developing control groups.

According to the present findings, children with ASD exhibited repetition suppression effects in response to both human and non-human action sounds, as previously found in neurotypical adults (Giusti et al., 2010; Pizzamiglio et al., 2005) and typically developing toddlers and children (see *Chapter 3*). They also presented with a similar time-course of human and non-human action sound processing over the frontal and temporal sites, as typically developing controls. In addition, no hemispheric lateralization differences were found between any of the groups for either human or non-human action sound processing. However, perceptual processing atypicalities over the parietal cortex were observed at an early stage of cognitive processing, for both human and non-human action sounds in children with ASD, when compared with both chronological age- and verbal age-matched controls. Such atypicalities in the neural processing of human and non-human action sounds extend previous research showing impairments in the visual processing of human actions (Bernier et al., 2007; Martineau et al., 2008; Oberman et al., 2005; Oberman, Ramachandran & Pineda, 2008), as well as enhancements in visual processing of non-social stimuli in individuals with ASD (Webb et al., 2006; see also McCleery, Stefanidou, & Graham, 2011).

Although the focus of the current study was not early sensory processing of action or non-action-related sounds, it is important to note that the ERP waveforms over the frontal and temporal cortices in both ASD and control groups presented with a similar

early processing pattern as the one observed in the typical development study presented in *Chapter 3,* and in previous neurotypical adult studies of action-related sound processing (e.g. Giusti et al., 2010). P1 and N1 components were found in both the ASD and control groups over the frontal and temporal channels respectively, and were elicited by both human and non-human action sounds, although the repetition suppression effect was larger for non-human action sounds. This finding replicates previous findings of an almost intact P1 response to speech sounds in children with ASD (Ceponiene et al., 2003). Interestingly, the current P1 peak latency analyses also revealed faster processing of repeated human action sounds in both the ASD group and chronological-age matched controls, possibly reflecting faster early detection of, or stronger habituation to, human action sounds in both groups (see also Guiraud et al., 2011). Notably, faster processing of repeated human action sounds over the frontal channels was found to be associated with higher non-verbal ability in children with ASD, whereas larger P1 and N1 cortical responses to non-repeated non-human action sounds over the frontal and temporal cortices were associated with more social communication difficulties, as scored during the administration of the ADOS. These correlations may reflect a potential relationship between early sensory processing of auditory human action stimuli with fine motor skills or non-verbal reasoning ability in children with ASD, which, however, warrants further investigation due to the small sample included in the current study. In addition, the positive correlation between early cortical responses to environmental or object sounds and ADOS communication scores may reflect the role of non-social neural processing in communication skills. This finding extends previous behavioural research findings revealing a positive correlation between repetitive behaviours and unusual visual exploration of objects at 12 months of age with later social and communication ADOS

scores at 36 months of age, in infants who were later diagnosed with ASD (Ozonoff et al., 2008).

Although this is the first study to use repetition suppression in children with ASD, previous studies using oddball ERP and MEG paradigms have revealed impaired P150 and M100 cortical responses to deviant tones presented within a stream of standard sounds in infants at risk for ASD and low-functioning children with autism (Guiraud et al., 2011; Tecchio et al., 2003). The intact P1 responses found in children with ASD in the present study may be related to differences in the experimental design employed here, with differences in the complexity and nature of the stimuli used, as well as with the chronological and developmental age of children with ASD included in the current study.

In terms of perceptual processing of human action sounds, the N4 and N600 components were identified within an early stage of cognitive processing over the frontal cortex in both the ASD and control groups. The N4 is thought to reflect semantic integration and has been previously found to be associated with gesture and speech processing in typically developing children and adults (e.g. Kim et al., 2006; Sheehan, Namy & Mills, 2007). In accordance with previous speech processing ERP findings in adults (Kim et al., 2006), in the present study, ERP responses to repeated human action sounds were more positive, whereas ERP responses to non-repeated human action sounds were more negative. Interestingly, a speech processing ERP study using an oddball paradigm (Whitehouse & Bishop, 2008) revealed atypical N4 responses to standard speech sounds in children with autism, when compared with typically developing children. However, when children were prompted to pay attention to the stimuli, no group differences were found. In addition, another speech processing study revealed that children with ASD, who showed an auditory preference for non-speech analogues

relative to "motherese" speech sounds on a behavioural task, also showed reduced cortical responses to speech (Kuhl et al., 2005).

The aforementioned findings highlight the importance of social attention for the neural processing of auditory social stimuli, such as speech or action-related sounds, and may provide a possible explanation for the current findings. More specifically, although no group differences were found for the N4 component over the frontal sites in the present study, an atypical N4 effect in response to repeated human action sounds was identified over the parietal cortex only in the ASD group. Based on Kuhl et al. (2005) findings, this larger negative activity in response to repeated human action sounds may be the result of reduced habituation to this stimulus type, possibly as a consequence of reduced attention to social stimuli, such as visual or auditory stimuli associated with human actions. These results extend recent behavioural research findings revealing poor habituation to faces in toddlers with ASD, which was also found to be correlated with ASD symptoms (Webb et al., 2010). They are also consistent with previous findings of an fMRI study showing reduced neural adaptation to faces in adults with ASD (Kleinhans et al., 2009). Moreover, the current results extend previous findings of Guiraud and colleagues (2011), who found that infants at risk for ASD showed a lack of habituation to pure tones at an earlier stage of sensory processing. The authors suggested that poor habituation to stimuli in the environment may be associated with both the "over-arousal" and the "under-arousal" theories described in ASD (Guiraud et al., 2011); in the first case, heightened arousal to specific stimuli in the environment may be the result of poor habituation, whereas in the second case, reduced habituation to certain stimuli may be associated with under-arousal and difficulties in associating old and new experiences and learning (Guiraud et al., 2011; see also Rogers & Ozonoff, 2005).

Along with reduced habituation to human action sounds, children with ASD also exhibited enhanced cortical responses to environmental sounds compared to typically developing controls. A negative component (N2b), which is thought to reflect processes associated with stimulus categorization (Luck, 2005), was identified over the parietal region in the ASD group, but was almost absent in the control groups. The N2b amplitude was larger in response to non-repeated non-human action sounds, possibly reflecting an enhanced non-social versus social stimulus categorization mechanism in children with ASD. These results are consistent with previous ERP findings revealing faster cortical responses to objects than faces in pre-school-age children with ASD (Webb et el., 2006) and in 10-month old siblings of children with ASD (McCleery et al., 2010). In addition, they extend previous behavioural research findings revealing enhanced non-social attention and visual or auditory preference for non-social stimuli, including objects and non-speech analogues (Klin, 1991; Klin et al., 2002b; Kuhl et al., 2005; Pierce et al., 2011; Shultz, Klin, & Jones, 2011). Although no correlations were found between the severity of ASD symptoms and non-social processing at this stage of cognitive processing, the relationship found between P1 responses to non-human action sounds and communication scores on the ADOS indicates that non-social preferences may play a key role in autism, possibly interfering with social communicative development in this population.

In summary, this is the first study to investigate the perceptual processing of auditory stimuli associated with human versus non-human actions in children with autism. In accordance with previous findings, the present study revealed both impaired social processing and enhanced non-social processing mechanisms in young children with ASD. The present findings support the notion that social impairments in ASD may

be associated not only with reduced social attention and deficient perceptual processing of social stimuli in the environment, but also a possible tendency to attend to non-social stimuli and/or enhanced non-social perceptual processing mechanisms, which may be present from an early age. However, due to the relatively small sample tested in the current study, as well as the lack of a final formal clinical diagnosis for some of the children in the ASD group, the present findings need to be replicated in a larger sample of children formally diagnosed with autism. In addition, the replication of the present results in ASD and typically developing groups of children matched for non-verbal age may exclude non-verbal ability as a potential factor associated with the perceptual processing of other people's actions or sounds produced by them.

On the other hand, in terms of the experimental design employed in the current study, a better understanding of habituation might be succeeded through the investigation of neural activation in response to both the first and the second stimuli presented in pairs in both children with autism and typically developing children. In addition, the use of a behavioural task assessing auditory preference for social versus non-social sounds and the investigation of the relationship between children's behavioural performance and brain activity in response to social versus non-social sounds might contribute to a deeper understanding of the relationship between social attention and social processing brain mechanisms in children with ASD (e.g., Kuhl et al., 2005). Similarly, attentional modulation during the ERP assessment might help us understand whether ERP responses in the ASD group are related to reduced attention to social stimuli or increased attention to non-social stimuli.

The present findings suggest that both social and non-social processing are atypical in autism, and may contribute to the development of research methodologies that may

further our understanding of the etiological mechanisms underlying these atypicalities in the future. In addition, the current data may have clinical implications for the development of intervention strategies for children with autism, targeting action and gesture imitation, as well as social attention and communication through the use of non-social means, such as objects (e.g. Ingersoll, 2010).

CHAPTER 5:

HUMAN AND NON-HUMAN ACTION SOUND PROCESSING IN TODDLERS AT RISK FOR AUTISM, TODDLERS WITH AUTISM SPECTRUM DISORDERS AND LOW-RISK TYPICALLY DEVELOPING TODDLERS

Abstract

Background: Previous research has revealed social attention deficits, as well as impairments in cortical responses to social stimuli, such as other people's actions or vocalizations, in infant siblings of children diagnosed with autism spectrum disorders (ASD). However, it is not currently known whether such atypicalities in neural activity are also present in response to non-vocal sounds produced by human actions versus environmental sounds in this population. **Method:** An auditory-auditory repetition suppression event-related potentials (ERPs) paradigm was employed and ERPs were recorded whereby toddlers at risk for ASD and low-risk controls passively listened to repeated versus non-repeated human action and environmental sounds. An additional set of analyses comparing high-risk toddlers with toddlers on the autism spectrum and low-risk controls was also conducted. **Results:** Human and non-human action-related sounds elicited atypical neural activity over temporal and parietal sites at an early stage of cognitive processing in the high-risk group. However, no significant group differences were found over the frontal or frontocentral channels. In analyses including toddlers who met behavioural criteria for an ASD on the standardised behavioural diagnostic measure used in this study, human action sound processing was reduced over the right frontal cortex in the ASD group, compared with low-risk controls. However, no processing differences for either human or non-human action sounds were found between the ASD and high-risk groups at a late stage of cognitive processing. **Conclusion:** The current results extend previous findings revealing atypical cortical responses to both social and non-social stimuli in young children with ASD and their siblings, and provide evidence for a shared ASD endophenotype between children with autism and their non-ASD toddler siblings.

5.1 Introduction

Autism is a pervasive developmental disorder, characterised by a "triad of impairments" in communication, social interaction, and restricted interests or repetitive behaviours (American Psychiatric Association, 2000), and cannot be reliably diagnosed until 3 years of age, except in cases where there are persistent and clear developmental delays from 24 months of age (Chawarska, Klin, Paul, Macari, & Volkmar, 2009; Chawarska, Klin, Paul, & Volkmar, 2007; Zwaigenbaum et al., 2009; see also, McCleery, Stefanidou & Graham, 2011). Although the genetic liability for ASD has been revealed by several genomic studies (Anney et al., 2010; Bucan et al., 2009; Miller et al., 2009), as well as familial risk (e.g. Bailey et al., 1998; Bolton et al., 1998; Piven et al., 1997a; Ritvo et al., 1989) and twin studies (e.g. Bailey et al., 1995; Folstein & Rutter, 1977; Steffenburg et al., 1989; see also Newschaffer et al., 2012), autism is still considered a behaviourally characterised disorder. In contrast to other genetically defined disorders presenting with an ASD behavioural phenotype, such as Fragile X syndrome (e.g. Brown et al., 1986), no single gene or specific gene-gene interactions have been associated with autism as a singular disorder (Newschaffer et al., 2012). In addition, the "triad of impairments" in ASD has been suggested to be "fractionable" in genetic research and etiology, with different genes seemingly associated with different aspects of the autism phenotype (Happe & Ronald, 2008).

The need for further investigation of the etiological mechanisms of autism and early diagnosis has given rise to the development of extensive longitudinal research on infant and toddler siblings of children diagnosed with ASD, who have been found to be at significantly higher risk of developing the disorder (up to 18.7%) (Ozonoff et al., 2011; see also, Rogers, 2009). Previous research on infant and toddler siblings of

children diagnosed with ASD has revealed language and motor delays (Gamliel et al., 2009; Iverson & Wozniak, 2007; Landa & Carrett-Mayer, 2006; Loh et al., 2007; Toth et al., 2007; Yirmiya et al., 2006; Zwaigenbaum et al., 2005), as well as impairments in social and communicative behaviours, such as response to name, social smiling, requesting behaviours, joint attention, and gestural communication (Bedford et al., 2012; Cassel et al., 2007; Cornew et al., 2012; Goldberg et al., 2005; Mitchell et al., 2006; Nadig et al., 2007; Presmanes et al., 2007; Rozga et al., 2011; Sullivan et al., 2007; Toth et al., 2007; Yoder et al. 2009; Zwaigenbaum et al., 2005). Critically, many such delays have also been found to exist even in those high-risk siblings of children with autism who did not develop the disorder themselves (Gamliel et al., 2009; Iverson & Wozniak, 2007; Mitchell et al., 2006; Toth et al., 2007). For example, Toth and colleagues (2007) found lower language ability, impaired adaptive behaviour, and impaired social communication skills, such as distal gesture use and social smiling, in non-autistic toddler siblings of children with ASD, when compared with toddlers with no family history of ASD. In addition, Mitchell et al. (2006) found that even high-risk siblings presenting with no ASD behavioural traits, used fewer gestures during play relative to low-risk siblings, at 18 months of age, according to parental reports.

Based on a recent hypothesis by Dawson, Bernier, and Ring (2012) that social and communication impairments in ASD may be driven by reduced attention to social stimuli or even enhanced attention to non-social stimuli in the environment (see also Dawson et al., 1998; Klin et al., 2002a; Klin et al., 2009; Mosconi et al., 2009; Pierce et al., 2011; Shultz, Klin & Jones, 2011), recent studies of infants and toddlers at risk for autism also investigated social attention in high-risk infant siblings at a very early age (e.g. Chawarska, Macari & Shic, 2013; Shic, Macari & Chawarska, 2013). For example,

Chawarska, Macari, and Shic (2013) reported that a group of 6-month old high-risk siblings, who were later diagnosed with ASD, spent less time looking to a social scene including an actress engaging in different actions. Similar results were reported by the same authors in another study using face stimuli (Shic, Macari, & Chawarska, 2013). Notably, other studies have revealed increased looking times to objects (Droucker, Curtin & Vouloumanos, 2013) and a preference for non-speech analogues (Curtin & Vouloumanos, 2013), as well as better working memory for non-social targets during a delayed-response task (Noland et al., 2009), in infant siblings of children with ASD. These findings are consistent with previous research showing atypical preference for, and visual exploration of, objects in high-risk infants relative to low-risk controls (Bhat, Galloway, & Landa, 2010; Koterba, Leezenbaum, & Iverson, 2012; Ozonoff et al., 2008), as well as a "sticky attention" to non-social targets and difficulties disengaging their attention from them (Elsabbagh et al., 2013; Elsabbagh et al., 2009b; Sacrey, Bryson & Zwaigenbaum, 2013; Zwaigenbaum et al., 2005).

The aforementioned findings of both impaired social attention and enhanced non-social preferences in infant siblings of children with ASD complement previous research evidence from electrophysiological and neuroimaging studies in this population for atypical neural processing of both social stimuli, such as faces (Fox et al., 2013; Key & Stone, 2012a; Key & Stone, 2012b), direct eye-gaze (Elsabbagh et al., 2009a), human vocalisations (Lloyd-Fox et al., 2013), and speech (Seery et al., 2012), and enhanced neural processing of non-social stimuli, such as objects (McCleery et al., 2009) or non-social sounds (Guiraud et al., 2011). For example, Lloyd-Fox et al. (2013) employed fNIRS in order to examine how 4- to 6-month old infants at risk for ASD process visual and auditory social stimuli (see also *Chapter 4, Section 4.1*). Visual

social stimuli included videos of female actors either moving their eyes or performing social games (e.g. “peekaboo” or “incy wincy spider”). Auditory stimuli comprised non-speech human vocalisations (a person crying, laughing, yawning or coughing), and non-social auditory stimuli, including environmental sounds (e.g., running water) or sounds produced by toys (e.g., rattles). The authors reported that high-risk infants exhibited decreased haemodynamic responses to videos of social stimuli over the temporal cortex compared to low-risk controls. In addition, Lloyd-Fox et al. (2013) findings revealed that non-speech vocalizations did not elicit significant haemodynamic responses over the temporal cortex in high-risk infants, as opposed to the low-risk group. However, neural responses to non-social sounds observed in high-risk infants tended to be more robust than those observed in the low-risk group (Lloyd-Fox et al., 2013).

Lloyd-Fox et al. (2013) findings provide preliminary evidence for atypical cortical processing of human actions and non-speech vocalizations in infant siblings of children with ASD. In addition, they extend previous findings from electrophysiological and neuroimaging studies revealing similar atypical cortical responses to biological motion and human actions in individuals with ASD (Bastiaansen et al., 2011; Dapretto et al., 2005; Kroger et al., 2013; Martineau et al., 2010; Oberman et al., 2005; Oberman, Ramachandran, & Pineda, 2008; see also, *Chapter 1, Sections 1.2.4, 1.2.5, & Chapter 4, Section 4.1*). Most importantly, they complement our previous ERP findings in children with ASD (see *Chapter 4*), who exhibited atypical cortical responses to both non-vocal human and non-human action-related sounds. However, very little is known about how toddlers at risk for ASD process auditory stimuli associated with non-vocal, human and non-human actions.

Based on our previous research findings in children with ASD, revealing an impaired human action sound processing mechanism, along with enhanced perceptual processing of environmental sounds in high-functioning children with ASD relative to typically developing controls (see *Chapter 4*), the aim of the current study was to investigate whether toddler siblings of children with ASD present with similarly atypical social and non-social auditory processing mechanisms. To this end, we employed the auditory-auditory repetition suppression ERP paradigm used in our previous studies (see *Chapters 3 and 4*), along with two separate sets of analyses. In the first set of analyses, high-risk toddler siblings, who did not present with full ASD symptomatology, were compared with chronological age and verbal age matched toddlers, who had an older typically developing sibling. In the second set of analyses, high-risk toddlers who did not present with full ASD symptoms were compared with chronological age matched low-risk controls, as well as toddlers with suspected ASD. By doing this, we aimed to further our understanding of the development of social processing mechanisms in 2- to 3-year old toddlers who are at risk of developing an ASD but who did not meet cut-off behavioural criteria for autism at the time of testing, relative to toddlers who met behavioural criteria for an autism spectrum disorder on the standardized Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2000).

Findings of the current study will extend a previous line of work revealing atypical social and non-social processing mechanisms in infants and toddlers at risk for ASD, which may be associated with social and communication difficulties observed in this population. In addition, they may provide insight into social and non-social processing similarities and differences between toddlers at risk for ASD and toddlers

who are on the autism spectrum, and therefore contribute to a better understanding of the ASD endophenotype.

Aims of the study

The aims of the present study were:

a) to examine whether toddler siblings of children with ASD exhibit repetition suppression effects in response to human and non-human action-related sounds, by showing differential responses to repeated versus non-repeated stimuli,
b) to investigate the neural time-course of human action sound processing in toddlers at risk for ASD and whether their neural responses to human action sounds are delayed or reduced, when compared with low-risk toddlers,
c) to investigate whether intact or enhanced neural responses are elicited by non-human action sounds in the high-risk group relative to controls,
d) to determine whether there are any lateralization differences for human or non-human action sound processing between the groups,
e) to examine all the aforementioned research questions in an additional group of toddlers with suspected ASD, when compared with high-risk toddlers who do not present with ASD behavioural traits, and typically developing, low-risk toddlers,
f) to examine the relationship between perceptual processing of action- and non-action-related sounds and language ability, nonverbal ability, social and communication skills, and ASD symptomatology as measured by the ADOS-G in all groups.

5.2 Method

5.2.1 Recruitment and Screening

Participants were recruited through the British Autism Study of Infant Siblings (BASIS) network in London, United Kingdom, and the "Peach" network for families with children with autism in Berkshire, United Kingdom. In addition, some families were recruited from the Birmingham, West Midlands, region of the United Kingdom, through the distribution of research subject recruitment flyers that have been specifically approved by the University of Birmingham Internal Review Board (IRB), as well as through visits at local parent support groups for parents of children with ASD and schools for children with special needs. Parents, who provided their contact details to the researchers of the Autism Research Group at the University of Birmingham, were contacted in order to be informed about studies that would be appropriate for their child's age and developmental level.

As long as parents verbally agreed for their child to take part in the current study, they visited the Infant and Child Lab at the University of Birmingham, where they were asked to read and sign a University of Birmingham Internal Review Board (IRB) approved consent form to approve their child's participation in the study (see *Appendices A4, A6*). Parents were also asked to complete a brief questionnaire and provide information about any medical complications during pregnancy or birth, issues related to their child's course of physical and neurological development, and/or any medication that was administered to their child (see *Appendices B1, B2*). Children who had experienced neurological problems, such as epilepsy, were excluded from participation in this study. Health-related problems that are not thought to affect a child's brain development, such as allergies, were not considered grounds for dismissal.

5.2.2 Study 1

5.2.2.1 Sample

Twenty-six toddler siblings of children diagnosed with an autism spectrum disorder (High-risk group; 17 males, 9 females) and twenty-two toddlers with no family history of autism (Low-risk group; 11 males, 11 females), aged 2- to 3-years, participated in the study. All participants in the low-risk group had an older typically developing sibling. Three high-risk toddlers (all males) and four low-risk toddlers (1 male, 3 females) were excluded from the analyses due to motor and ocular motor artifacts in the ERP data. Although none of the participants had a diagnosis of an autism spectrum disorder, five high-risk toddlers (4 males, 1 female) were excluded from this analysis due to their high scores on the ADOS-G (see *Section 5.2.2.2* below). These toddlers met criteria for an autism spectrum disorder on the ADOS and were included in the second experimental analysis of the current study, described below (see *Section 5.2.3*). Therefore, the current analyses are based on ERP data from 18 high-risk toddlers (HR; 10 males, 8 females), who did not meet criteria for an autism spectrum disorder when assessed using the ADOS-G, and 18 low-risk toddlers (LR; 10 males, 8 females), individually matched for gender, chronological age, and verbal ability (see *Table 8,* for group characteristics). Independent samples *t*-tests revealed that there were no significant differences between the groups in terms of chronological age (HR group: M=31.6, S.E.=1.32; LR group: M=29.7, S.E.=1.08, $t(34)=1.14$, $p>0.05$), equal variances assumed (see *Table 8)*. None of the children taking part in this study had a history of seizures or any other neurological disorder, or any hearing problems. Information related to handedness was not collected, as most parents were unsure about

their child's preference at this early age. There were no bilingual toddlers in the current sample, except for one participant in the high-risk group.

5.2.2.2 Behavioural measures

Autism Diagnostic Observation Schedule-Generic (ADOS-G)

The Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord et al., 2000) was used for the behavioural characterization of all toddlers in the HR group and the verification of diagnosis in their older siblings. All older siblings had a formal clinical diagnosis of an ASD, apart from 4 children who were in the process of receiving a formal community diagnosis. Although the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter & Le Couteur, 1994) has been found to differentiate even toddlers with ASD from those who were never suspected of being on the autism spectrum (Lord, Luyster, Guthrie, & Pickles, 2012) and diagnostic specificity has been suggested to improve when both the ADI-R and the ADOS-G are used (Kim & Lord, 2012), its use in this study was not possible due to time limitations. However, the ADOS-G alone was found to have a higher predictive value, when compared with the combination of ADOS-G and ADI-R in a large sample of 20- to 40-month old children at high risk for ASD (Oosterling et al., 2010). Additionally, more recent findings revealed that the ADOS-G predicted developmental trajectories of both positive and negative ASD symptomatology in toddlers as young as 15 months of age (Lord et al., 2012).

Only two of the high-risk toddlers that took part in this study were referred to a clinician for an ASD or a speech and language assessment prior to participation in the study. One of those toddlers met criteria for an autism spectrum disorder on the ADOS-

G, and was consequently excluded from the current analysis. As mentioned above, the current analysis was based on data from 18 high-risk toddlers with viable ERP data, who did not meet criteria for an ASD on the ADOS-G assessment (see *Table 8*, for mean ADOS scores). The remaining five toddlers who met criteria for ASD on the ADOS-G were included in a smaller sample of 2- and 3-year old toddlers, who met criteria for ASD on the ADOS-G, and were compared with high-risk toddlers, not suspected of ASD, and low-risk toddlers, in an additional set of analyses (see *Section 5.2.3*, below). In addition, all older siblings of high-risk toddlers met criteria for an ASD on the ADOS-G assessment, apart from a 5-year old and an 8-year old child, who had been formally diagnosed with Asperger's Disorder and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), respectively, at an earlier age.

Language and cognitive assessments

The Mullen Scales of Early Learning (MSEL; Mullen, 1995) were used for the assessment of verbal and non-verbal abilities for each of the toddlers in both groups. Verbal ability measures were used in order to match the groups for verbal age. Group comparisons revealed no significant verbal age equivalent differences between the high-risk (M=30.9 months, $S.E.$=1.26) and the low-risk groups (M=33.5 months, $S.E.$=1.84), $t(34)$=-1.15, p>0.05, equal variances assumed (see *Table 8,* for characteristics of participants).

The MacArthur-Bates Communicative Development Inventory: Words and Sentences form (CDI-II; Fenson et al., 1993) was also used as an additional verbal ability measure, and was completed by parents of all participants except for one toddler in the low-risk group (see also, *Table 8*). This measure was used in order to investigate

further whether there were any language ability differences between the groups, based on parents' reports. Independent samples *t*-tests revealed no significant group differences with regard to the number of words used by high- and low-risk toddlers, reported on the CDI-II (HR group: *M*=432.9, *S.E.*=40.21; LR group: *M*=451.3, *S.E.*=45.55, $t(33)=-0.3$, $p>0.05$, equal variances assumed (see also *Table 8*).

Verbal and non-verbal ability measures were also used in order to investigate potential relationships between brain activity associated with human or non-human action sound processing and verbal or non-verbal skills in both toddlers at risk for autism and low-risk controls.

Quantitative Checklist for Autism in Toddlers (Q-CHAT)

The Quantitative Checklist for Autism in Toddlers (Q-CHAT; Allison et al., 2008; see also *Appendix B4*) is a screening tool for social and communication difficulties associated with ASD in toddlers and was completed by parents of all participants, except for two toddlers in the low-risk group. The Q-CHAT was used in order to screen for social and communication difficulties in low- and high-risk toddlers and investigate whether there were significant differences between the groups. Independent samples *t*-tests did not reveal any significant differences between the Q-CHAT scores of the high-risk (*M*=18.6, *S.E.*=2.06) and the low-risk groups (*M*=23.2, *S.E.*=1.91), $t(32)=-1.63$, $p>0.05$, equal variances assumed (see *Table 8*). The relationship between brain activity, elicited by human and non-human action sounds, and scores on the Q-CHAT was also examined in both groups.

Characteristics	HR group (*n*=18)	LR group (*n*=18)	Group comparison (P-value)
Gender	10 males, 8 females	10 males, 8 female	N/A
Chronological age (months)	31.6 (5.6) range: 24 - 41	29.7 (4.6) range: 23 - 39	0.26
MSEL-Verbal age (months)	30.9 (5.3) range: 26.5 - 47	33.5 (7.8) range: 23 - 55	0.26
MSEL-Non-Verbal age (months)	34.3 (9.3) range: 25 - 55.5	32.5 (7.2) range: 20.5 - 50.5	0.51
CDI-II (words)	432.9 (170.6) (range: 86 - 648)	*n=17* 451.3 (187.8) range: 93 – 636	0.76
Q-CHAT	18.6 (8.6) range: 2 - 42	*n=16* 23.2 (7.6) range: 13 - 38	0.11
ADOS-Communication subscale	1.7 (0.9)	N/A	N/A
ADOS-Social subscale	1.3 (1.9)	N/A	N/A
ADOS- Total score	2.8 (2.4)	N/A	N/A

Table 8. *Characteristics of high-risk and low-risk groups, matched for gender, chronological age and verbal age - Means (S.D.) and the results of group comparisons, based on independent samples t-tests.*

5.2.3 Study 2

5.2.3.1 Sample

As part of the current study, a second set of analyses was conducted comparing three groups of toddlers. The first group included 2- and 3-year old toddlers who met criteria for an autism spectrum disorder on the ADOS-G (n=13). However, none of these toddlers had received a formal community diagnosis at the time of testing and were either younger siblings of children diagnosed with ASD (n=5) or did not have any older siblings (n=8). Parents of toddlers with suspected ASD were asked to sign a different IRB approved consent form (see *Appendix A5*). The first group of toddlers with suspected ASD was compared with two gender- and chronological age-matched groups: a) high-risk toddlers, who did not meet criteria for an ASD on the ADOS-G (n=13), and b) low-risk toddlers (n=13). The mean chronological age of the ASD group was 33.5 months (*S.E.*=1.95), which was not significantly different from the mean chronological ages of the high-risk group (M= 33.4 months, *S.E.*=1.53) or the low-risk group (M= 32.5 months, *S.E.*=1.73), $F(2,36)=0.11$, $p<0.05$ (see *Table 9*, for group characteristics). In accordance with the inclusion and exclusion criteria described in Section 5.2.1, none of the toddlers who took part in this study experienced any neurological disorders or hearing problems. In addition, there were no bilingual participants in the high- and low-risk groups, although the ASD group included three bilingual toddlers. It is important to note, however, that the stimuli used in the current study were non-vocal and, therefore, it was not anticipated that second language exposure should affect neural processing of stimuli in the current study.

5.2.3.2 Behavioural measures

All participants completed the same behavioural measures outlined in section 5.2.2.2. Table 9 shows the characteristics and the means of the results from the behavioural assessments completed by all groups, as well as the significance levels of any observed group differences. Only one toddler in the ASD group failed to complete the Mullen Scales of Early Learning, due to severe behavioural difficulties and lack of responsiveness to the examiner, and his verbal age was acquired through the administration of the Vineland Adaptive Behaviour Scales (VABS; Sparrow, Cicchetti & Balla, 2005) to the parents. In addition, two families in the low-risk group did not complete the CDI-II and the Q-CHAT, which was also not completed by two families in the ASD group. Although, groups were not matched for verbal age in the additional / secondary set of analyses, cognitive and social skills assessments were used in order to investigate the relationship between brain activity and verbal or non-verbal ability, as well as between brain activity and social and communication skills.

Characteristics	ASD (*n*=13)	HR group (*n*=13)	LR group (*n*=13)	Group comparison (*P*-value)
Gender	9 males, 4 females	9 males, 4 females	9 males, 4 females	N/A
Chronological age (months)	33.5 (7) range: 24 - 46	33.4 (5.5) range: 24 - 41	32.5 (6.3) range: 24 - 47	0.9
MSEL Verbal age (months)	*(n=12)* 18.7 (8.6) range: 9.5 - 32.5	31.7 (6.1) range: 26.5- 47	36.7 (7.9) range: 23 - 55	0.00
MSEL Non-Verbal age (months)	*(n=12)* 23.9 (7) range: 15 - 36.5	36.5 (10.1) range: 25- 55.5	36.1 (7.9) range: 23.5-50.5	0.001
CDI-II (words)	144.9 (192.5) range: 0 - 572	416.1 (189.5) range: 86 - 648	*(n=11)* 528.8 (147.7) range: 138 - 636	0.00
Q-CHAT	*(n=11)* 41.7 (18.4) range: 15 - 67	20.1 (8.1) range: 8 - 42	*(n=11)* 21.3 (7.4) range: 13 - 36	0.00
ADOS-Communication subscale	5.2 (2) range: 2 - 8	1.6 (0.8) range: 0 - 3	N/A	0.00
ADOS-Social subscale	8.9 (2.8) range: 4 - 13	1.5 (2) range: 0 - 6	N/A	0.00
ADOS-Total score	14 (4.4) range: 7 - 19	2.9 (2.3) range: 0 - 7	N/A	0.00

Table 9. *Characteristics of ASD, high-risk and low-risk groups, matched for gender and chronological age - Means (S.D.) and results of group comparisons, based on one-way analyses of variance.*

5.2.4 Stimuli- Experimental procedure

The ERP assessment utilised in the present study was based on a novel auditory-auditory repetition suppression ERP paradigm that included a single block of approximately 570 trials, lasting for 30 minutes and presenting two types of sounds: human action (e.g., hands clapping, hands ripping paper) and non-human action (helicopter blades spinning, ocean waves) -related sounds. Each type of sound was followed by a sound from either the same or the other perceptual category, resulting in four trial types: a) congruent (repeated) human action-related sound trial, b) incongruent (non-repeated) human action-related sound trial, c) congruent (repeated) non-human action-related sound trial, and d) incongruent (non-repeated) non-human action-related sound trial (see also, *Chapter 2, Sections 2.3, 2.4*).

5.2.5 ERP Recording and Analysis

Brain electrical activity was recorded continuously using a child-friendly, high-density, 128-channel Hydrocel Geodesic Sensor Net (HCGSN, Electrical Geodesics Inc., Eugene, Oregon) (Tucker, 1993). EEG was referenced to a single vertex electrode, Cz (sample rate = 500 Hz). All bioelectrical signals were recorded using EGI NetStation amplifiers with an input impedance of less than 100 kΩ.

EEG data were band-pass filtered offline at 0.1 to 40 Hz and segmented to epochs, using NetStation 4.2 software (Electrical Geodesics). Epochs were time-locked to the second auditory stimulus in the trial, contained 100 ms pre-stimulus time and 700 ms post-stimulus time, and were organised by stimulus type [human action sound repetition (congruent), human action sound non-repetition (incongruent), non-human action sound repetition (congruent), non-human action sound non-repetition

(incongruent)]. Data were then processed using an artifact-detection tool, which marked channels bad, if the recording was poor for greater than 99 % of the time (threshold maximum-minimum, >150), and segments if they contained more than 12 bad channels, eye-blinks or eye-movements. Following this automated artifact detection process, individual examination of each of the trials by a trained EEG researcher was also performed in order to remove trials including any remaining ocular or motor artifacts from the data. All toddlers produced a minimum of 40 viable ERP trials per experimental condition, apart from two high-risk toddlers who had 31 to 38 artifact-free trials per condition, and one low-risk toddler who had 33 to 46 artifact-free trials per condition, and were included in both analyses. Tables 10 and 11 show the means of motor and ocular-motor artifact-free trials per condition, per group, for both analyses. Planned contrasts revealed that the numbers of artifact-free trials per condition were not significantly different between the groups (see *Tables 10, 11*, for significance levels). Bad channels in trials with 12 or fewer bad channels and no artifacts were replaced using a spherical spline interpolation algorithm (Srinivasan et al., 1996). Finally, individual subject data were averaged, re-referenced to an average reference, and baseline-corrected to a 100 ms prestimulus interval.

Condition	HR group (*n*=18)	LR group (*n*=18)	Group comparison (*P*-value)
Human action sounds			
Congruent	67.3 (21.6)	60.3 (13.9)	0.26
Incongruent	66.1 (20.2)	60.2 (17.7)	0.36
Non-Human action sounds			
Congruent	65.3 (22.3)	59.9 (15.3)	0.4
Incongruent	66.8 (17.5)	60.1 (15.7)	0.24

Table 10. *Descriptive data - Means (S.D.) of artifact-free trials per condition in chronological and verbal age-matched high-risk and low-risk groups, and the results of group comparisons, based on independent samples t-tests.*

Condition	ASD (*n*=13)	High-risk (*n*=13)	Low-risk (*n*=13)	Group comparison (*P*-value)
Human action sounds				
Congruent	63.2 (21.3)	65.8 (23.9)	59.7 (14.8)	0.75
Incongruent	65.5 (22)	64.5 (21.4)	60.5 (19.2)	0.74
Non-Human action sounds				
Congruent	66.9 (21.1)	62.7 (24.7)	61.2 (18.5)	0.79
Incongruent	64.6 (22.6)	65.9 (19.1)	60.3 (16)	0.81

Table 11. *Descriptive data - Means (S.D.) of artifact-free trials per condition in chronological age-matched ASD, high-risk and low-risk groups, and the results of group comparisons, based on one-way analyses of variance.*

Electrode locations and time windows for analysis in the current study were selected based on findings of the typical development and ASD studies described in Chapters 3 and 4, on previous speech processing findings of ERP studies using oddball paradigms in individuals with ASD (e.g. Ceponiene et al., 2003; Kuhl et al., 2005; Lepisto et al., 2005; Lepisto et al., 2006), and on visual inspection of grand average ERP data, prior to any statistical analysis. Electrode sites that were selected for both sets of analyses included 27 frontal (9 left, 9 middle, 9 right) and 24 parietal electrodes (8 left, 8 middle, 8 right) electrodes (see *Figures 23a, b*). However, the electrode sites selected for analysis over the temporal cortex differed in the two sets of analyses. In the first analysis comparing chronological and verbal age matched high-risk and low-risk groups of toddlers, 18 temporal electrodes (9 left, 9 right) were selected for analysis; whereas in the second analysis, the selected electrode array over the temporal sites included 14 electrodes (7 left, 7 right) in total (see *Figures 23c, d*). Averaged ERPs obtained during all experimental conditions were analysed sample by sample in the 50-700 ms temporal window by using repeated-measures Analysis of Variance (ANOVA) and paired contrasts using bonferroni correction, in order to identify similarities or differences in repetition suppression effects in response to human action- versus non-human action-related sounds between the groups. Different time windows for human and non-human action sound processing over frontal, temporal and parietal electrode sites were selected for analysis. A comparison of the mean amplitude of the major ERP components between conditions and groups was conducted. In addition, the peak latency of some of the components was analysed, in order to examine timing processing differences between the groups.

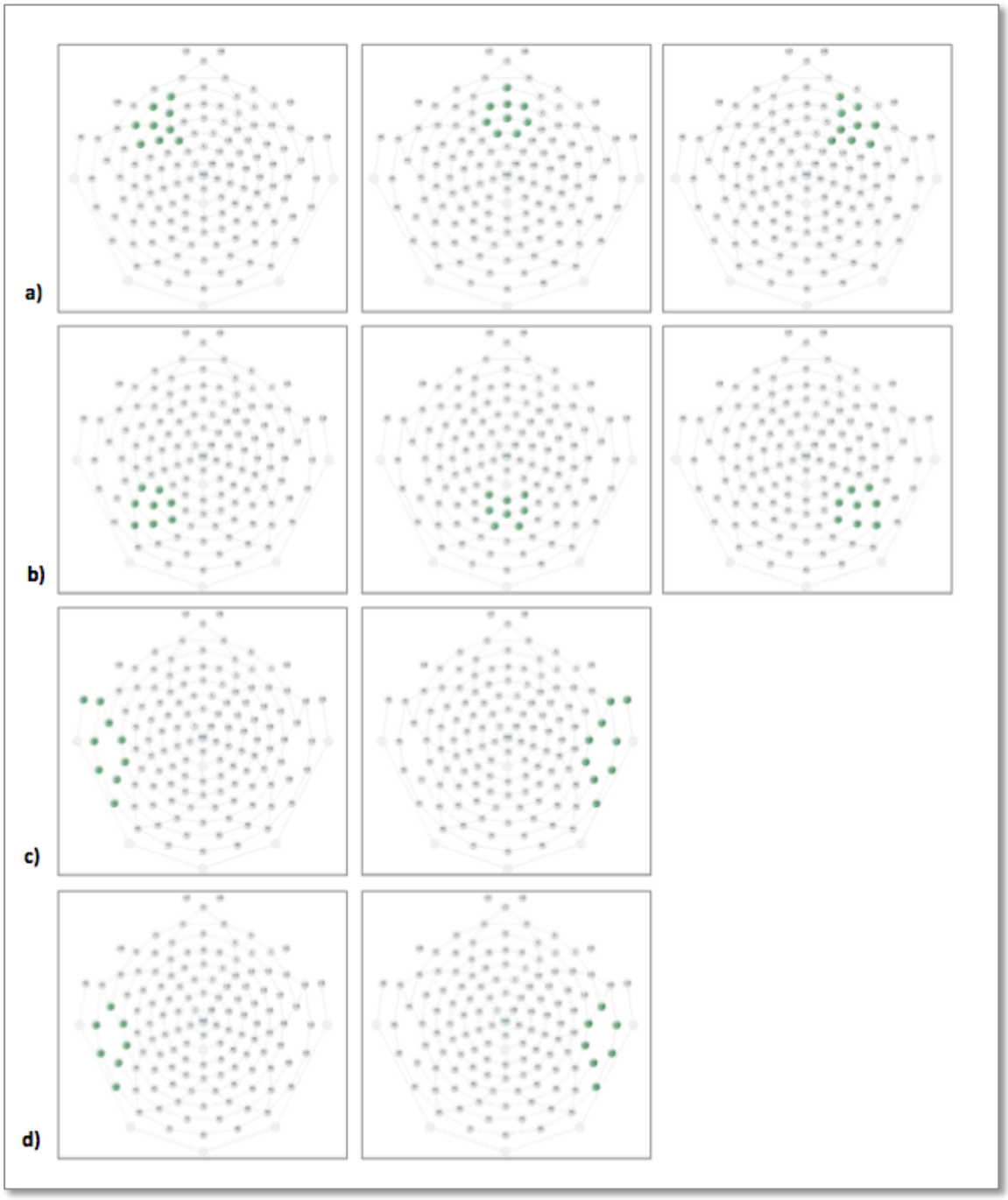

Figure 23. *Montage selected for analysis in the HR, LR and ASD groups.*

a) Left, middle, and right frontal electrodes selected for the ERP data analyses. b) Left, middle, and right parietal electrodes selected for the ERP data analyses, c) Left and right temporal electrodes selected for the ERP data analyses in Study 1, comparing toddlers at risk for autism with low-risk toddlers, and d) Left and right temporal electrodes selected for the ERP data analyses in Study 2, comparing toddlers with high ADOS scores with toddlers at risk for autism, not suspected of ASD, and low-risk toddlers.

5.3 Results

5.3.1 Study 1: High-risk (n=18) vs Low-risk group (n=18)

ERPs to human action sounds included two early sensory processing components (P1, N1), an early component reflecting stimulus feature mismatch cortical responses (P2), and three later perceptual processing components (P3, N4, N620). ERPs to non-human action sounds included the P1 and N1 components for both groups and a N4 component only for the high-risk group. P1 and N1 (50-170ms) peaked at approximately 110 ms for both stimulus types over the frontal and temporoparietal channels respectively, whereas P2 was identified within the time window 180-300 ms over the frontal cortex. In addition, the N4 (420-540ms) and P3 (420-540ms) components were identified for human action sounds over the frontal and temporal sites respectively in both groups, whereas an additional N4 (300-500ms) component was also identified over the parietal sites for non-human action sounds in the high-risk group. Finally, N620 (540-700ms) was identified over the frontal region in both groups.

A between-subjects, repeated-measures ANOVA with stimulus type (human action sound, non-human action sound), condition (congruent/repeated stimuli, incongruent/non-repeated stimuli) and hemisphere (left, middle, right) as within-subjects factors, and group (HR, LR) as between-subject factor was carried out on the mean amplitude of all ERP components and the peak latency of the P1 and N1 components. However, only interactions between stimulus type and condition, revealing significant repetition suppression effects, were considered for follow-up analyses, which included pairwise comparisons using Bonferroni correction, in order to explore ANOVA interactions further. In addition, the relationship between cortical responses to both human and non-human action sounds and chronological age, as well as cognitive

ability and social communication skills in both groups was explored by conducting correlation analyses between the mean amplitude and peak latency of the selected components and chronological age in months, as well as scores achieved on the standardised behavioural measures and questionnaires employed in the current study. The latter included the age equivalents in months on all the MSEL subscales (visual reception, fine motor, receptive language and expressive language), the verbal and non-verbal age equivalents in months (mean scores on verbal and non-verbal ability MSEL scales), the scores on all the ADOS-G subscales (communication, reciprocal social interaction, imagination/creativity, stereotyped behaviours and restricted interests), the ADOS-G communication and social interaction total scores, the Q-CHAT scores and the CDI-II scores (total number of words). However, the results from the correlation analyses were viewed with caution due to the large number of factors included in the analysis and the small sample recruited in the present study.

Frontal activity

P1 (P110: 50-170ms)

A between-subjects, repeated-measures ANOVA carried out on the P1 mean amplitude revealed a significant interaction between stimulus type and condition, $F(1,34)=19.86$, $p<0.001$. Paired contrasts using Bonferroni correction showed that this interaction was driven by greater P1 responses to non-repeated ($M=1.87\mu V$, $S.E.=0.25$) relative to repeated ($M=0.77\mu V$, $S.E.=0.23$) non-human action sounds over the frontal channels, $p<0.001$ (see *Figure 24*). In addition, the investigation of the relationship between the P1 mean amplitude and cognitive and social skills revealed a significant negative correlation between the P1 amplitude in response to non-repeated non-human

action sounds and verbal age in the LR group, r=-.54, p<0.05 (receptive language: r=-.55, p<0.05; expressive language: r=-.46, p=0.05). A between-subjects, repeated-measures ANOVA carried out on the P1 peak latency revealed no significant main effects or interactions.

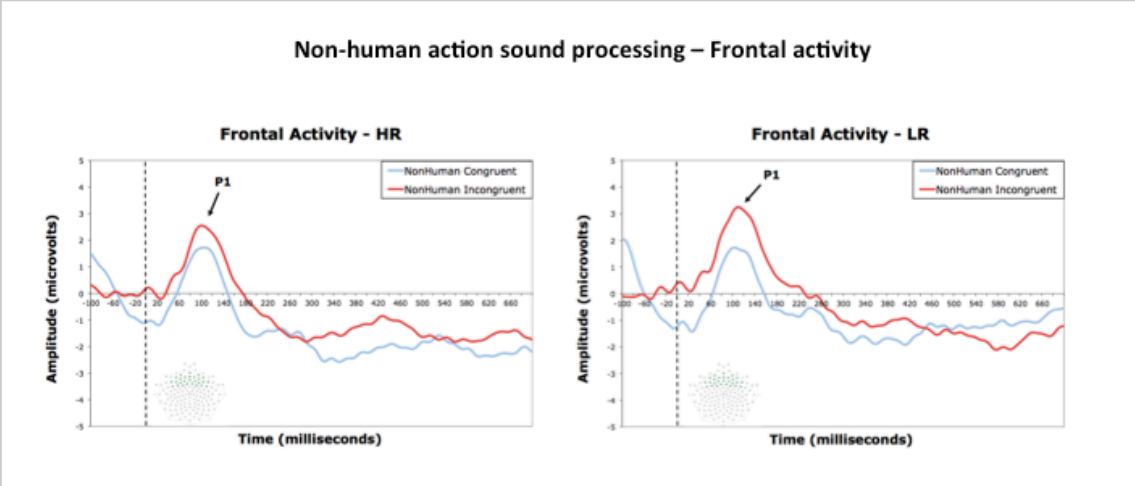

Figure 24. *Repetition suppression waveforms recorded over the frontal cortex for non-human action sounds in the HR and LR groups.*

P2 (P240: 180-300ms)

A between-subjects, repeated-measures ANOVA was carried out on the P2 mean amplitude and revealed a significant effect of stimulus type (F(1,34)=26.74, p<0.001) and a significant interaction between stimulus type and condition (F(1,34)=6.54, p<0.05) (see *Figure 25*). However, pairwise comparisons using Bonferroni correction revealed only a marginally significant difference between the P2 amplitude in response to repeated (M=0.94μV, $S.E.$=0.28) and non-repeated (M=0.22μV, $S.E.$=0.33) human action sounds, p=0.07.

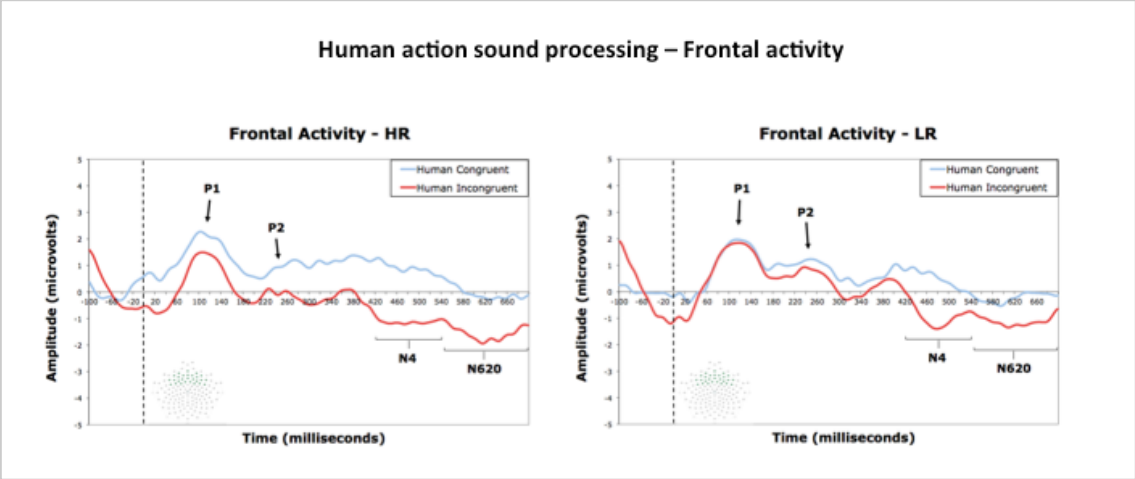

Figure 25. *Repetition suppression waveforms recorded over the frontal cortex for human action sounds in the HR and LR groups.*

N4 (N480: 420-540ms)

A between-subjects, repeated-measures ANOVA conducted on the N4 mean amplitude revealed a significant effect of stimulus type ($F(1,34)=11.27$, $p<0.01$), a significant effect of condition ($F(1,34)=4.52$, $p<0.05$), and a significant interaction between stimulus type and condition ($F(1,34)=9.71$, $p<0.01$). Paired contrasts using Bonferroni correction revealed that this effect was driven by a greater N4 amplitude in response to non-repeated (M=-1.04μV, $S.E.$=0.35) relative to repeated (M=0.69μV, $S.E.$=0.45) human action sound stimuli, $p<0.01$ (see *Figure 25*).

N620 (540-700ms)

A between-subjects, repeated-measures ANOVA conducted on the N620 amplitude revealed a significant effect of stimulus type ($F(1,34)=5.23$, $p<0.05$), and a significant effect of hemisphere ($F(2,68)=3.67$, $p<0.05$). However, the interaction between stimulus type and condition was not found to be significant, $F(1,34)=3.08$, $p=0.09$ (see *Figure 25*).

Temporal activity

N1 (N110: 50-170ms)

A between-subjects, repeated-measures ANOVA conducted on the N1 mean amplitude revealed a significant effect of hemisphere ($F(1,34)=4.47$, $p<0.05$) and a significant interaction between stimulus type and condition ($F(1,34)=9.84$, $p<0.01$). Paired contrasts using Bonferroni correction showed that the latter was driven by greater N1 responses to non-repeated (M=-1.25μV, $S.E.$=0.18) relative to repeated (M=-0.72μV, $S.E.$=0.16) non-human action sounds over the temporal channels, $p<0.05$ (see *Figure 26)*. In addition, the investigation of the relationship between the N1 mean amplitude and cognitive and social skills revealed a significant positive correlation between the N1 amplitude in response to non-repeated non-human action sounds and ADOS communication scores in the HR group, r=.48, $p<0.05$. A between-subjects, repeated-measures ANOVA carried out on the N1 peak latency revealed no significant main effects or interactions.

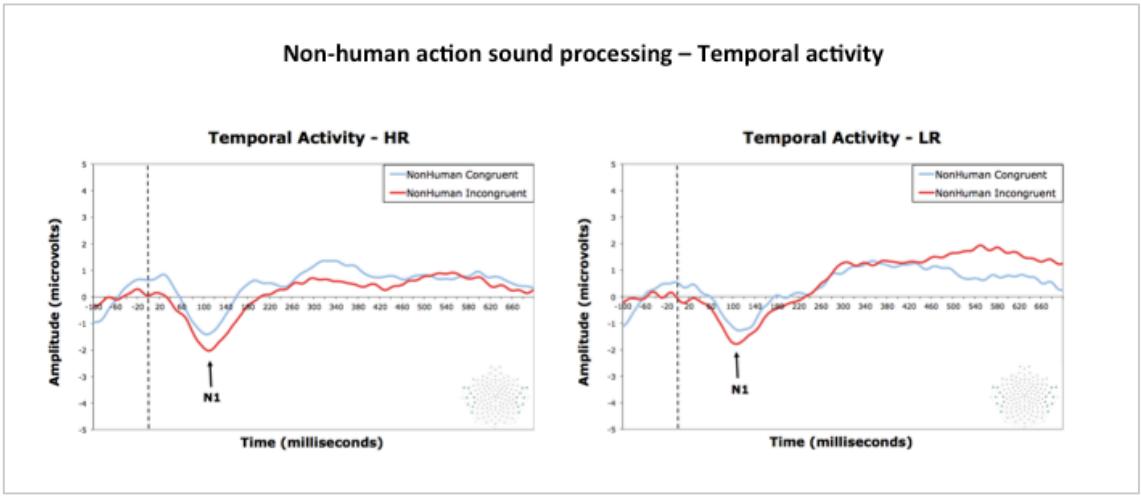

Figure 26. *Repetition suppression waveforms recorded over the temporal cortex for non-human action sounds in the HR and LR groups.*

P3 (P480: 420-540 ms)

A between-subjects, repeated-measures ANOVA carried out on the P3 mean amplitude revealed a significant effect of stimulus type ($F(1,34)=5.22$, $p<0.05$), condition ($F(1,34)=5.88$, $p<0.05$) and hemisphere ($F(1,34)=8.91$, $p<0.01$), and a marginally significant interaction between stimulus type, condition and group ($F(1,34)=3.81$, $p=0.06$). Paired contrasts using Bonferroni correction showed that this interaction was driven by a more negative P3 amplitude in response to repeated (M=-1.96μV, $S.E.$=0.45) relative to non-repeated (M=0.16μV, $S.E.$=0.52) human action sounds over the temporal channels in the HR group, $p<0.01$ (see *Figure 27*). However, a one-sample t-test revealed that the P3 amplitude in response to repeated human action sounds in the HR group was not significantly different from 0, $t(17)=-1.95$, $p=0.07$.

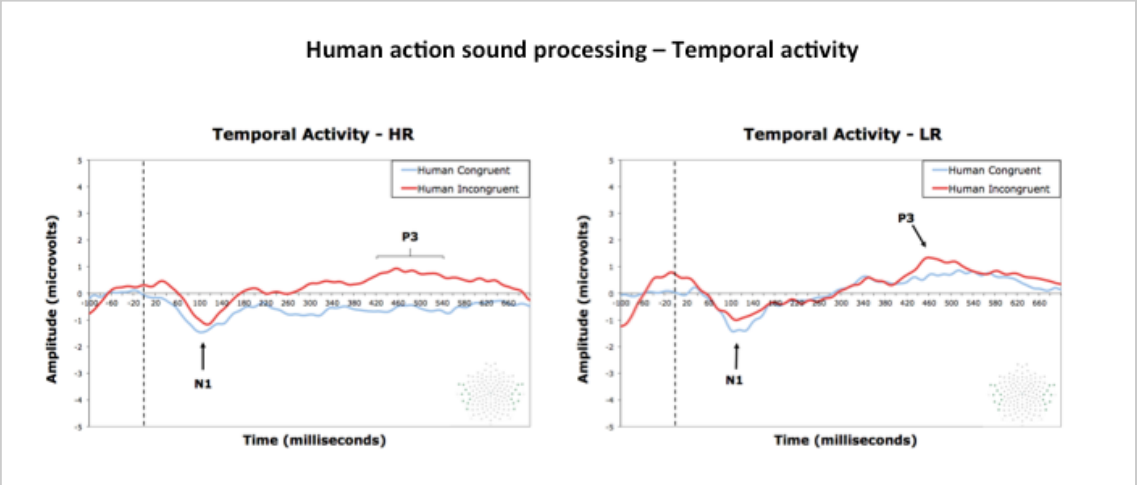

Figure 27. *Repetition suppression waveforms recorded over the temporal cortex for human action sounds in the HR and LR groups.*

Parietal activity

N1 (N110: 50-170ms)

No significant main effects or interactions were revealed by repeated-measures analyses of variance carried out on the N1 mean amplitude or peak latency over the parietal cortex (see *Figures 28, 29*).

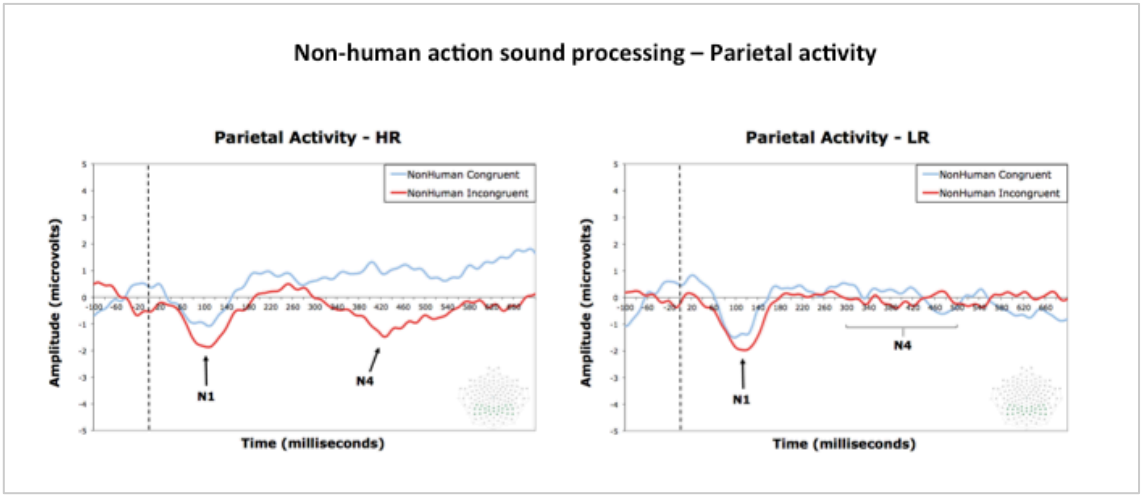

Figure 28. *Repetition suppression waveforms recorded over the parietal cortex for non-human action sounds in the HR and LR groups.*

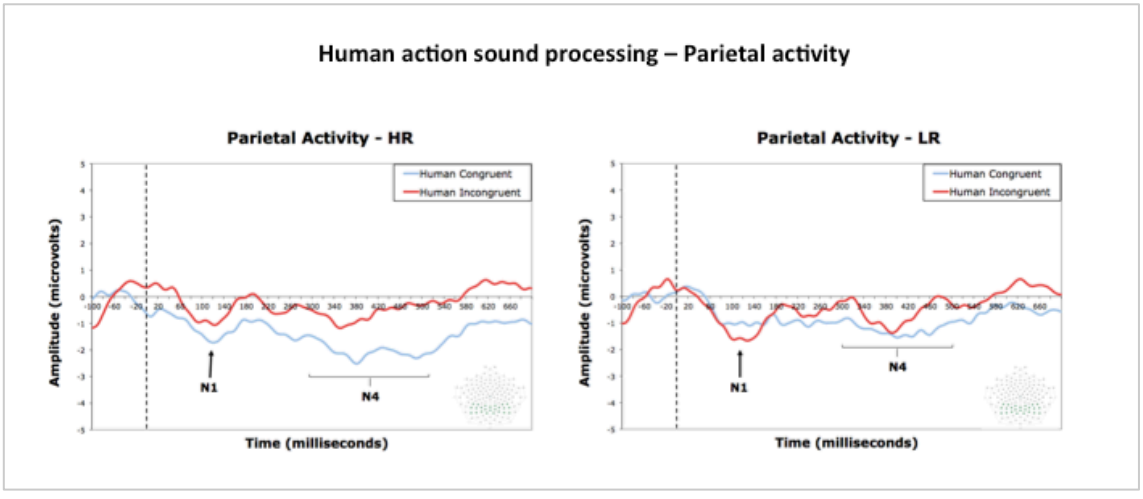

Figure 29. *Repetition suppression waveforms recorded over the parietal cortex for human action sounds in the HR and LR groups.*

N4 (N400: 300-500ms)

A between-subjects, repeated-measures ANOVA conducted on the parietal N4 mean amplitude revealed a significant effect of stimulus type ($F(1,34)=12.61$, $p=0.001$) and hemisphere $F(2,68)=16.27$, $p<0.001$), a significant interaction between stimulus type and condition ($F(1,34)=11.79$, $p<0.01$), and a significant interaction between stimulus type, condition and group ($F(1,34)=4.26$, $p<0.05$). Paired contrasts using Bonferroni correction revealed that this effect was driven by a larger difference between N4 mean amplitude in response to repeated ($M=0.97\mu V$, *S.E.*=0.51) and non-repeated ($M=-0.79\mu V$, *S.E.*=0.5) non-human action sound stimuli in the HR group, $p<0.01$ (see *Figures 28, 30*). The investigation of the relationship between N4 responses to non-human action sounds with cognitive and social skills revealed a positive correlation between N4 mean amplitude in response to repeated non-human action sounds and ADOS creativity/imagination scores in the HR group ($r=.71$, $p=0.001$), and a positive correlation between N4 mean amplitude in response to repeated non-human action sounds and QCHAT scores in the LR group ($r=.51$, $p<0.05$).

In addition, based on the results in children with ASD (presented in the previous chapter), human action sound processing within this stage of processing over the parietal cortex was explored further. Although no group differences were found for the parietal N4 in response to human action sounds in the current study, paired samples *t*-tests revealed significant differences between N4 responses to repeated ($M=-2.08\mu V$, *S.E.*=0.5) versus non-repeated ($M=-0.66\mu V$, *S.E.*=0.45) human action sounds in the HR group ($t(17)=-2.43$, $p<0.05$), but no significant differences for the same comparison in the LR group (Repeated: $M=-1.25\mu V$, *S.E.*=0.44, Non-repeated: $M=-0.62\mu V$, *S.E.*=0.55, $t(17)=-0.99$, $p=0.34$) (*see Figure 29*). The analysis of the relationship between social

and communication skills and the N4 amplitude in response to repeated human action sounds revealed that the latter was negatively correlated with ADOS creativity/imagination scores in the HR group, r=-.51, p<0.05.

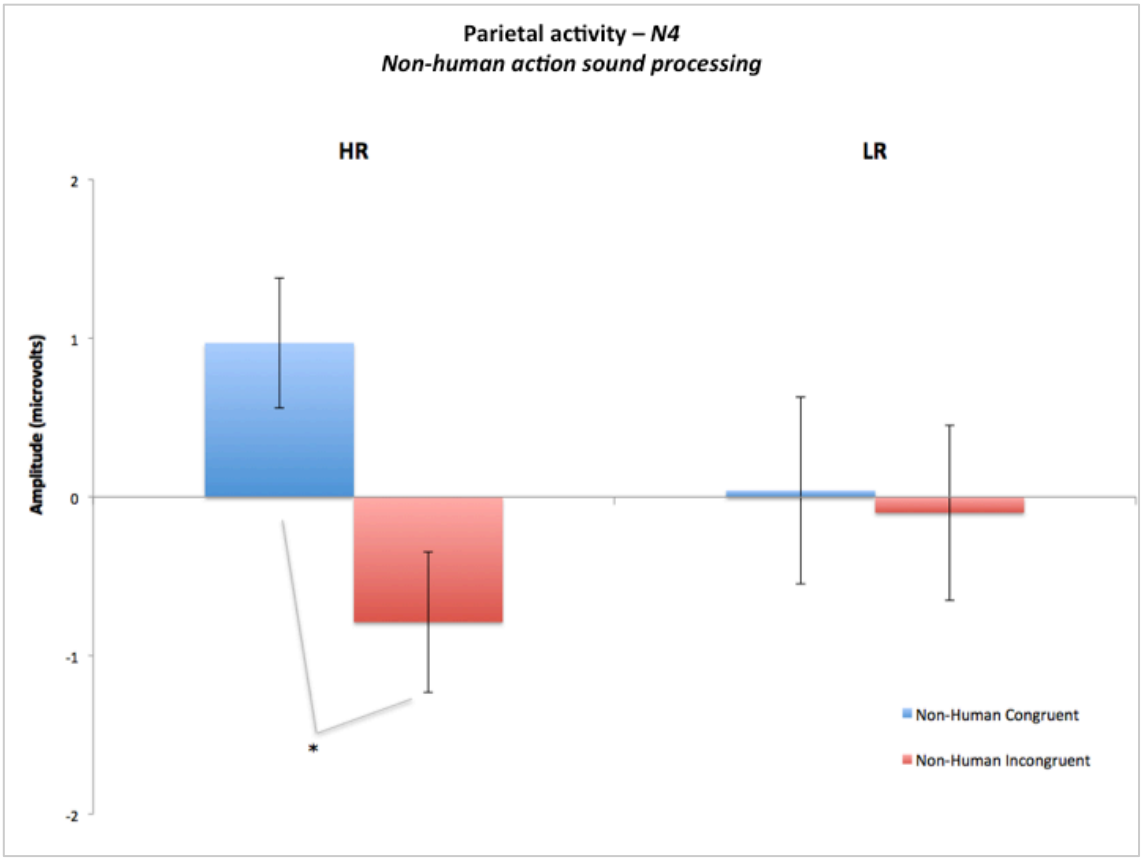

Figure 30. *N4 mean amplitude in response to repeated and non-repeated non-human action sounds over the parietal cortex in the HR and LR groups.*

5.3.2 Study 2

The same ERP components were selected for the investigation of human and non-human action sound processing in high-risk toddlers who did not meet criteria for an ASD on the ADOS-G (HR group; n=13), when compared with toddlers who met the criteria for an ASD (ASD group; n=13), and low-risk typically developing toddlers (LR

group; *n*=13). The ASD group was also compared directly with the LR group. All groups were matched for gender and chronological age.

In accordance with the first set of analyses, a between-subjects, repeated-measures ANOVA with stimulus type (human action sound, non-human action sound), condition (congruent, incongruent) and hemisphere (left, middle, right) as within-subjects factors, and group (HR vs LR, HR vs ASD, ASD vs LR) as a between-subjects factor, was carried out on the mean amplitude of all the ERP components selected for analysis, as well as on the peak latency of the P1 and N1 components. The reason why the analysis was conducted using pairwise comparisons is because we aimed to directly compare the high-risk group with the chronological age-matched low-risk group, as previously done in the first set of analyses for the comparison of chronological and verbal age-matched groups. However, it is important to note the increased likelihood of Type 1 error in the current analysis approach, as opposed to the analyses of variance including all three groups. Therefore, the latter was also completed and revealed the same results, which, however, are not presented her for the reasons mentioned above. In addition, the relationship between the mean amplitude or peak latency of the selected ERP components and social and cognitive skills was also explored in the ASD group, as previously described for the high-risk and low-risk groups in *Section 5.3.1.* As the ERP waveforms of the high-risk and low-risk groups were similar with the ERP waveforms of the same groups presented in the previous section of this chapter (*n*=18), only the ERP waveforms of the ASD group are shown in the following results section.

5.3.2.1 HR versus LR group

Frontal activity

P1 (P110: 50-170ms)

A between-subjects, repeated-measures ANOVA conducted on the P1 mean amplitude revealed a significant interaction between stimulus type and condition, $F(1,24)=13.71$, $p=0.001$, driven by greater P1 responses to non-repeated ($M=1.93\mu V$, $S.E.=0.32$) relative to repeated ($M=0.92\mu V$, $S.E.=0.29$) non-human action sounds over the frontal channels, $p<0.05$ (Bonferroni correction). A between-subjects, repeated-measures ANOVA carried out on the P1 peak latency revealed no significant main effects or interactions.

P2 (P240: 180-300ms)

A between-subjects, repeated-measures ANOVA carried out on the P2 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=19.86$, $p<0.001$), a significant interaction between stimulus type and hemisphere ($F(2,48)=4.3$, $p<0.05$) and a marginally significant interaction between stimulus type and condition ($F(1,24)=35.45$, $p=0.057$). Pairwise comparisons using Bonferroni correction revealed that the latter was driven by a greater P2 amplitude elicited by repeated ($M=0.92\mu V$, $S.E.=0.37$) versus non-repeated ($M=-0.08\mu V$, $S.E.=0.41$) human action sounds, $p=0.05$.

N4 (N480: 420-540ms)

A between-subjects, repeated-measures ANOVA conducted on the N4 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=6.33$, $p<0.05$), a significant effect of condition ($F(1,24)=4.28$, $p<0.05$), a significant interaction between

stimulus type and condition ($F(1,24)=12.51$, $p<0.01$), and a significant interaction between stimulus type, condition and hemisphere ($F(2,48)=5.39$, $p<0.01$). Paired contrasts using Bonferroni correction revealed that this effect was driven by a greater N4 amplitude in response to non-repeated (Middle: $M=-1.59\mu V$, *S.E.*=0.49; Right: $M=-1.51\mu V$, *S.E.*=0.47) relative to repeated (Middle: $M=1.15\mu V$, *S.E.*=0.55; Right: $M=1.03\mu V$, *S.E.*=0.61) human action sound stimuli over the middle ($p=0.001$) and right ($p<0.01$) frontal cortex.

N620 (540-700ms)

A between-subjects, repeated-measures ANOVA conducted on the N620 amplitude revealed a significant interaction between stimulus type and condition ($F(1,24)=7.23$, $p<0.05$), which was driven by larger N620 responses to non-repeated ($M=-1.42\mu V$, *S.E.*=0.43) relative to repeated ($M=0.21\mu V$, *S.E.*=0.65) human action sounds, $p<0.05$.

Temporal activity

N1 (N110: 50-170ms)

A between-subjects, repeated-measures ANOVA carried out on the N1 mean amplitude revealed a significant effect of stimulus ($F(1,24)=7.05$, $p<0.05$) and a significant interaction between stimulus type and condition ($F(1,24)=9.76$, $p<0.01$). Paired contrasts using Bonferroni correction showed that this interaction was driven by greater N1 responses to non-repeated ($M=-1.53\mu V$, *S.E.*=0.22) relative to repeated ($M=-0.95\mu V$, *S.E.*=0.21) non-human action sounds over the temporal channels, $p=0.05$. A

repeated analysis of variance conducted on the N1 peak latency revealed no significant main effects or interactions.

P3 (P480: 420-540 ms)

A between-subjects, repeated-measures ANOVA carried out on the P3 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=5.2$, $p<0.05$) and hemisphere ($F(1,24)=6.71$, $p<0.05$), and a significant interaction between stimulus type and condition ($F(1,24)=5.51$, $p=0.05$). Paired contrasts using Bonferroni correction showed that this interaction was driven by a significant difference between P3 amplitude in response to repeated (M=-0.21μV, *S.E.*=0.25) and non-repeated (M=0.95μV, *S.E.*=0.35) human action sounds over the temporal channels, $p<0.01$.

Parietal activity

N1 (N110: 50-170ms)

No significant main effects or interactions were revealed by repeated-measures analyses of variance carried out on the N1 mean amplitude over the parietal cortex. However, a between-subjects, repeated-measures ANOVA conducted on the parietal N1 latency revealed a significant interaction between stimulus type, condition and hemisphere, $F(2,48)=5.79$, $p<0.01$, driven by faster N1 responses to non-repeated human (M=100.02*ms*, *S.E.*=5.6) versus non-human (M=124.72μV, *S.E.*=7.26) action sounds over the left hemisphere, $p<0.05$. However, pairwise comparisons using Bonferroni correction did not reveal any significant differences between the N1 latency to repeated and non-repeated human or non-human action sound stimuli.

N4 (N400: 300-500ms)

A between-subjects, repeated-measures ANOVA conducted on the parietal N4 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=16.03$, $p=0.001$) and hemisphere $F(2,48)=8.54$, $p=0.001$), a significant interaction between stimulus type and condition ($F(1,24)=12.71$, $p<0.01$), and a significant interaction between stimulus type, condition and group ($F(1,24)=6.6$, $p<0.05$). Paired contrasts using Bonferroni correction revealed that this effect was driven by a larger difference between the N4 mean amplitude in response to repeated ($M=1.19\mu V$, *S.E.*=0.52) and non-repeated ($M=-0.79\mu V$, *S.E.*=0.51) non-human action sound stimuli in the HR group, $p<0.05$. In addition, in accordance with the first set of analyses conducted in the HR group, pairwise comparisons using Bonferroni correction revealed significant differences between N4 responses to repeated ($M=-2.26\mu V$, *S.E.*=0.5) versus non-repeated ($M=-0.32\mu V$, *S.E.*=0.54) human action sounds in the HR group ($p<0.05$), but no significant differences for the same comparison in the LR group (Repeated: $M=-1.62\mu V$, *S.E.*=0.5; Non-repeated: $M=-0.47\mu V$, *S.E.*=0.54; $p=0.11$).

5.3.2.2 HR versus ASD group

Frontal activity

P1 (P110: 50-170ms)

A between-subjects, repeated-measures ANOVA was carried out on the P1 mean amplitude and revealed a significant effect of hemisphere ($F(2,48)=5.17$, $p<0.05$) and a significant interaction between stimulus type and condition ($F(1,24)=9.83$, $p<0.01$). Paired contrasts using Bonferroni correction showed that this interaction was driven by greater P1 responses to non-repeated ($M=1.98\mu V$, *S.E.*=0.37) relative to repeated

(M=1.03μV, $S.E.$=0.3) non-human action sounds over the frontal channels, p<0.05. Figure 31 shows the repetition suppression waveforms recorded over the frontal cortex for both human and non-human action sounds in toddlers with ASD (see also *Figure 24*). In addition, the investigation of the relationship between the P1 mean amplitude and cognitive and social skills in the ASD group revealed a significant positive correlation between the P1 amplitude in response to repeated non-human action sounds and developmental age on the expressive language MSEL subtest, r=.68, p<0.05.

A repeated-measures ANOVA conducted on the P1 peak latency also revealed a significant interaction between stimulus type, condition, hemisphere and group, F(2,48)=4.47, p<0.05. However, pairwise comparisons did not reveal any significant differences between the P1 latency to repeated and non-repeated human or non-human action sound stimuli. The interaction was driven by faster responses to repeated non-human action sounds over the left (M=80.4*ms*, $S.E.$=11.16) relative to the middle (M=90.91*ms*, $S.E.$=9.69) frontal cortex in the ASD group, p<0.05 (Bonferroni correction) (see *Figure 31*). Correlation analyses also revealed a significant negative correlation between the P1 peak latency in response to repeated non-human action sounds and developmental age on the visual reception MSEL subtest in the ASD group, r=-.59, p<0.05. However, no other main effects or interactions were found for the P1 peak latency.

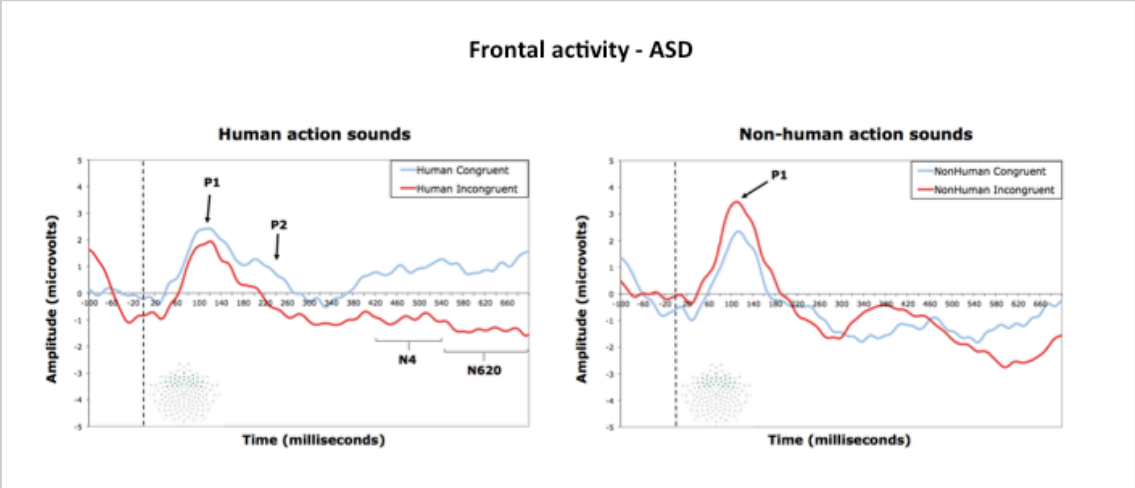

Figure 31. *Repetition suppression waveforms recorded over the frontal cortex for human and non-human action sounds in the ASD group.*

P2 (P240: 180-300ms)

A between-subjects, repeated-measures ANOVA carried out on the P2 mean amplitude revealed a significant effect of stimulus type, $F(1,24)=11.74$, $p<0.01$. However, the interaction between stimulus type and condition was not significant, $F(1,24)=2.64$, $p=0.12$.

N4 (N480: 420-540ms)

A between-subjects, repeated-measures ANOVA conducted on the N4 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=11.27$, $p<0.01$), a significant effect of condition ($F(1,34)=8.22$, $p<0.05$), and a significant interaction between stimulus type and condition ($F(1,24)=6.8$, $p<0.05$). Paired contrasts using Bonferroni correction revealed that this effect was driven by a greater N4 amplitude in response to non-repeated ($M=-1.09\mu V$, $S.E.=0.48$) relative to repeated ($M=0.83\mu V$, $S.E.=0.57$) human action sound stimuli, $p<0.01$ (see *Figures 25, 31)*. In addition, the investigation of the relationship between the N4 mean amplitude and social and

cognitive skills in the ASD group revealed a significant negative correlation between the N4 amplitude in response to repeated human action sounds and verbal age, r=-.58, p<0.05.

N620 (540-700ms)

A between-subjects, repeated-measures ANOVA conducted on the N620 amplitude revealed a significant effect of stimulus type (F(1,24)=9.34, p<0.01) and hemisphere (F(2,48)=3.36, p<0.05), and a significant interaction between stimulus type and condition (F(1,24)=5.04, p<0.05). The latter was driven by a larger N620 amplitude elicited by non-repeated (M=-1.42μV, $S.E.$=0.47) relative to repeated (M=0.51μV, $S.E.$=0.67) human action sounds, p<0.05 (Bonferroni correction) (see *Figures 25, 31)*.

Temporal activity

N1 (N110: 50-170ms)

A between-subjects, repeated-measures ANOVA carried out on the N1 mean amplitude revealed a significant interaction between stimulus type and condition (F(1,24)=16.64, p<0.001). Paired contrasts using Bonferroni correction showed that this interaction was driven by greater N1 responses to non-repeated (M=-1.51μV, $S.E.$=0.22) relative to repeated (M=-0.92μV, $S.E.$=0.23) non-human action sounds (p<0.05). Figure 32 shows the repetition suppression waveforms recorded over the temporal cortex for both human and non-human action sounds in toddlers with ASD (see also *Figure 26*). However, N1 amplitude was larger in response to repeated (M=-1.39μV, $S.E.$=0.16) versus non-repeated (M=-0.84μV, $S.E.$=0.18) human action sounds (p<0.01) over the temporal channels. The N1 peak latency analysis revealed no significant main effects or interactions.

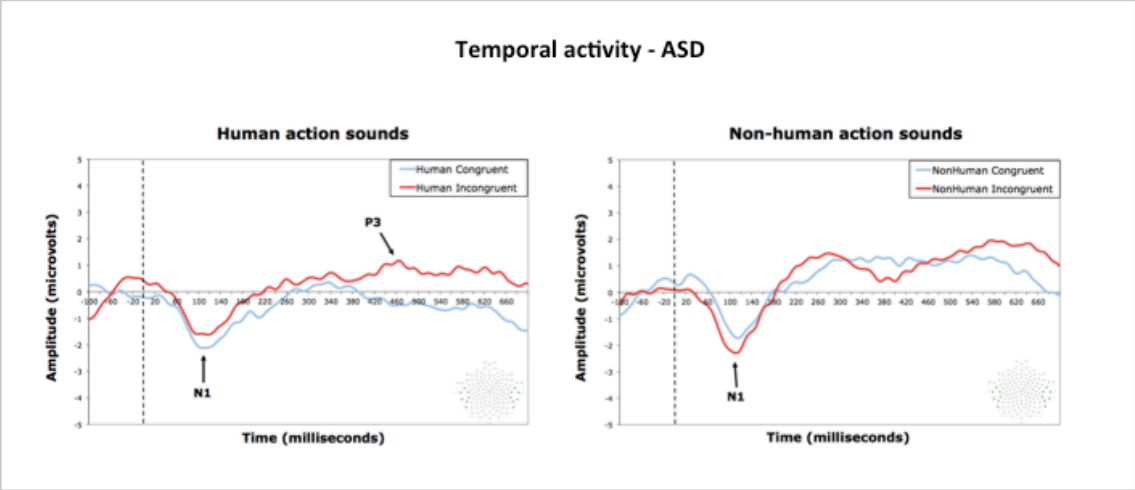

Figure 32. *Repetition suppression waveforms recorded over the temporal cortex for human and non-human action sounds in the ASD group.*

P3 (P480: 420-540 ms)

A between-subjects, repeated-measures ANOVA carried out on the P3 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=16.22$, $p=0.001$), condition ($F(1,24)=5.33$, $p<0.05$) and hemisphere ($F(1,24)=5.82$, $p<0.05$), and a significant interaction between stimulus type and condition ($F(1,24)=4.56$, $p<0.05$). Paired contrasts using Bonferroni correction showed that this interaction was driven by a significant difference between the P3 responses to repeated ($M=-0.65\mu V$, $S.E.=0.21$) and non-repeated ($M=0.83\mu V$, $S.E.=0.4$) human action sounds over the temporal channels, $p<0.01$ (see *Figures 27, 32)*.

Parietal activity

N1 (N110: 50-170ms)

No significant main effects or interactions were revealed by repeated-measures analyses of variance carried out on the N1 mean amplitude or peak latency over the parietal cortex. Figure 33 shows the repetition suppression waveforms recorded for both

human and non-human action sounds over the parietal cortex in toddlers with ASD (see also *Figures 28, 29*).

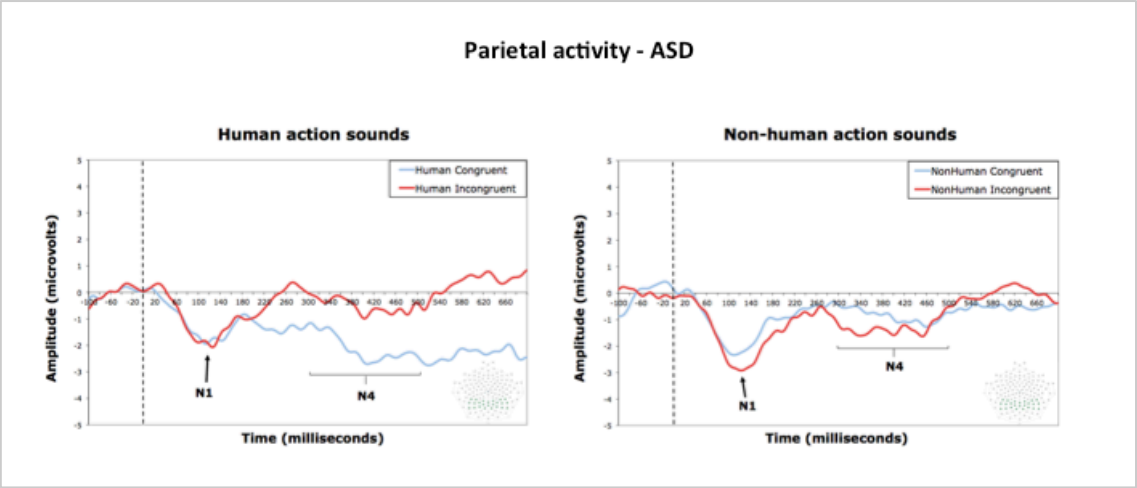

Figure 33. *Repetition suppression waveforms recorded over the parietal cortex for human and non-human action sounds in the ASD group.*

N4 (N400: 300-500ms)

A between-subjects, repeated-measures ANOVA conducted on the parietal N4 mean amplitude revealed a marginally significant effect of stimulus type ($F(1,24)=4.22$, $p=0.05$), a significant effect of hemisphere $F(2,48)=12.05$, $p<0.001$), and a significant interaction between stimulus type and condition ($F(1,24)=16.24$, $p<0.001$). Paired contrasts using Bonferroni correction revealed that this interaction was driven by a larger N4 mean amplitude in response to repeated (M=-2.18μV, $S.E.$=0.4) relative to non-repeated (M=-0.42μV, $S.E.$=0.37) human action sound stimuli ($p=0.001$), and in response to non-repeated (M=-1.06μV, $S.E.$=0.5) relative to repeated (M=0.16μV, $S.E.$=0.36) non-human action sounds ($p<0.05$) (see *Figures 28, 29, 33)*. The investigation of the relationship between N4 responses to human and non-human action sounds with cognitive and social communication skills in the ASD group revealed a

positive correlation between N4 mean amplitude in response to non-repeated non-human action sounds and developmental age on the receptive language MSEL subtest (r=.58, p<0.05).

5.3.2.3 ASD vs Low-risk group

Frontal activity

P1 (P110: 50-170ms)

A between-subjects, repeated-measures ANOVA conducted on the P1 mean amplitude revealed a significant interaction between stimulus type and condition, $F(1,24)=9.68$, $p=0.01$, driven by greater P1 responses to non-repeated (M=2.12μV, $S.E.$=0.36) relative to repeated (M=1.12μV, $S.E.$=0.29) non-human action sounds over the frontal channels, p<0.01 (Bonferroni correction) (see *Figures 24, 31)*. The P1 peak latency analysis revealed no significant main effects or interactions.

P2 (P240: 180-300ms)

A between-subjects, repeated-measures ANOVA carried out on the P2 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=11.72$, p<0.01). However, no other effects or interactions were found to be significant.

N4 (N480: 420-540ms)

A between-subjects, repeated-measures ANOVA conducted on the N4 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=7.35$, p<0.05), a significant effect of condition ($F(1,24)=8.86$, p<0.01), a significant interaction between stimulus type and condition ($F(1,24)=6.39$, p<0.05), and a significant interaction

between stimulus type, condition, hemisphere and group (F(1.6,37.6)=7.49, p<0.01). Paired contrasts using Bonferroni correction revealed that this effect was driven by a significant difference in the N4 amplitude elicited by non-repeated (M=-1.85μV, $S.E.$=0.76) relative to repeated (M=1.25μV, $S.E.$=0.74) human action sound stimuli over the right (p<0.01) frontal cortex in the LR group (see *Figures 25, 31, 34*). Additionally, within-subjects analyses of variance conducted in the low-risk group revealed a significant effect of condition (F(1,12)=6.71, p<0.05), a significant interaction between stimulus and condition (F(1,12)=8.81, p<0.05), and a significant interaction between stimulus, condition and hemisphere (F(1.38, 16.58)=6.87, p<0.05). However, the same analysis in the ASD group revealed only a significant effect of stimulus (F(1,12)=5.02, p<0.05).

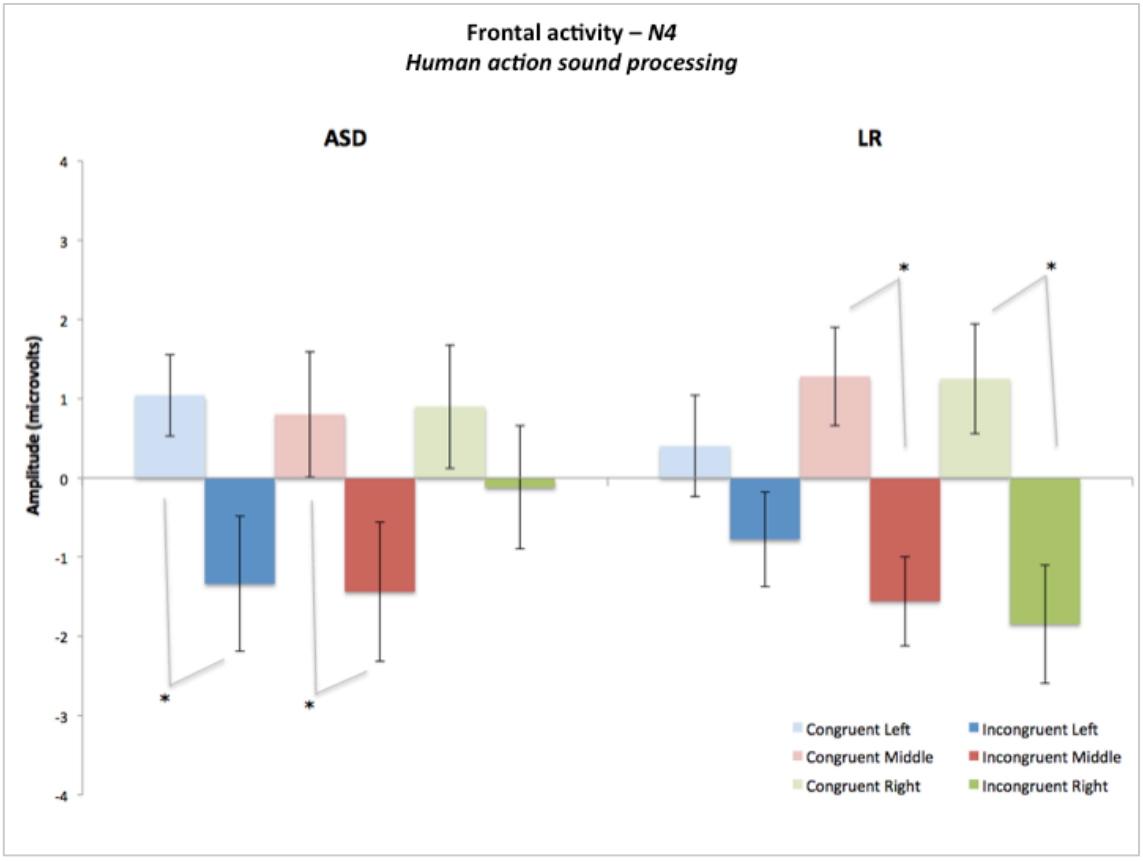

Figure 34. *N4 mean amplitude in response to repeated and non-repeated human action sounds over the left, middle and right frontal cortex in the ASD and LR groups.*

N620 (540-700ms)

A between-subjects, repeated-measures ANOVA conducted on the N620 amplitude revealed a significant effect of stimulus type ($F(1,24)=6.05$, $p<0.05$) and condition ($F(1,24)=16.64$, $p<0.001$), and a significant interaction between stimulus type, condition, hemisphere and group ($F(1.58,37.97)=5.96$, $p<0.01$). In accordance with the N4 results, the latter was driven by larger N620 responses to non-repeated (M=-1.76μV, $S.E.$=0.71) relative to repeated (M=0.55μV, $S.E.$=0.76) human action sounds over the right frontal cortex in the LR group, $p<0.05$ (see *Figures 25, 31).*

Temporal activity

N1 (N110: 50-170ms)

A between-subjects, repeated-measures ANOVA carried out on the N1 mean amplitude revealed a significant effect of hemisphere ($F(1,24)=6.14$, $p<0.05$), significant interaction between stimulus type and group ($F(1,24)=4.42$, $p<0.05$), and a significant interaction between stimulus type and condition ($F(1,24)=6.7$, $p<0.05$). Paired contrasts using Bonferroni correction showed that this interaction was driven by greater N1 responses to non-repeated (M=-1.42μV, $S.E.$=0.21) relative to repeated (M=-0.94μV, $S.E.$=0.18) non-human action sounds over the temporal channels, $p<0.05$ (see *Figures 26, 32*). The N1 peak latency analysis revealed no significant main effects or interactions.

P3 (P480: 420-540 ms)

A between-subjects, repeated-measures ANOVA carried out on the P3 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=8.67$, $p<0.01$), a

marginally significant effect of condition ($F(1,24)=4.17$, $p=0.05$) and a significant effect of hemisphere ($F(1,24)=7.38$, $p<0.05$). However, the interaction between stimulus type and condition was not found to be significant, $F(1,24)=2.16$, $p=0.15$.

Parietal activity

N1 (N110: 50-170ms)

No significant main effects or interactions were revealed by repeated-measures analyses of variance carried out on the N1 mean amplitude and peak latency over the parietal cortex.

N4 (N400: 300-500ms)

A between-subjects, repeated-measures ANOVA conducted on the parietal N4 mean amplitude revealed a significant effect of stimulus type ($F(1,24)=4.91$, $p<0.05$) and hemisphere $F(2,48)=12.09$, $p<0.001$) and a marginally significant effect of condition ($F(1,24)=4.23$, $p=0.05$). However, no significant interactions were found for this comparison.

5.4 Discussion

In the current study, we examined the perceptual processing of human versus non-human action sounds in high-risk toddler siblings of children with ASD compared to low-risk toddler siblings of typically developing individuals. An additional set of analyses including a group of toddlers, who met cut-off behavioural criteria for an autism spectrum disorder on the ADOS-G, also allowed for the comparison of non-ASD

high-risk toddlers with toddlers with suspected ASD, as well as for the comparison of the latter with low-risk typically developing toddlers.

Study 1

The first set of analyses included 2- to 3-year old high-risk toddlers, compared to low-risk toddlers, matched for chronological and verbal age. The results revealed that the time-course of human and non-human action sound processing over the frontal and temporal cortices was similar between the groups. In accordance with previous findings in neurotypical adults (Giusti et al., 2010) and findings in typically developing children and children with ASD presented in Chapters 3 and 4, non-human action sound repetition suppression effects were observed within an early stage of sensory processing (P1, N1) over frontal and temporal sites in both groups. On the other hand, human action sound processing was associated with later cognitive processing-related components (N4, P3) observed over the same region. However, a larger N4 repetition suppression effect in response to non-human action sounds was observed over the parietal sites in the high-risk group, compared to controls. These results are consistent with previous findings in children with ASD (see *Chapter 4*), who also exhibited enhanced non-human action sound processing mechanisms.

In regards to the perceptual processing of human action sounds, both groups exhibited repetition suppression effects within a processing stage (N4) that has been found to be associated with semantic integration and gesture and speech processing in typically developing children and adults (e.g. Kim et al., 2006; Sheehan, Namy & Mills, 2007). Interestingly, children with ASD have been found to exhibit reduced N4 effects in response to streams of standard speech sounds, when they were not required to pay

attention to them (Whitehouse & Bishop, 2008). In addition, McCleery et al. (2010) examined semantic integration in children with ASD and observed reduced category mismatch effects in response to social stimuli (pictures followed by words), as reflected in the N4 amplitude over central-parietal channels. However, non-social category mismatch N4 effects were found to be intact in the ASD group in the same study (McCleery et al., 2010). In the current study, no group differences were observed for the N4 component over the frontal cortex, as both the high- and low-risk groups exhibited significant repetition suppression effects in response to human action sounds. However, there was a trend for more negative responses to repeated human action sounds over the temporal cortex in the high-risk group, possibly reflecting less habituation to auditory social stimuli. These results extend previous fNIRS findings by Lloyd-Fox et al. (2013), who reported atypicalities in neural activity over the temporal cortex elicited by non-speech vocalizations in 4- to 6-month old infant siblings of children with ASD. Although the stimuli used in the Lloyd-Fox et al. (2013) study included only adult vocalisations, whereas the social stimuli used in the current study included only hand action sounds, together these findings provide evidence for a trend for atypical processing of sounds produced by other people's body actions in infant and toddler siblings of children diagnosed with ASD.

With respect to non-human action sound processing, both groups exhibited significant repetition suppression effects within an early stage of sensory processing, as reflected by greater P1 and N1 mean amplitudes in response to non-human action sounds, preceded by human action sounds over frontal and temporal sites, respectively. These results did not replicate Guiraud et al. (2011) findings, which revealed impairments in "predictive coding" mechanisms within an early stage of auditory

processing (P150) in 9-month old high-risk infants. Guiraud and colleagues (2011) reported that high-risk infants exhibited less habituation to standard (repeated) pure tones, as reflected in the P150 peak amplitude. These differences may reflect developmental changes across the age groups assessed by Guiraud et al. (2011) and in the present study. Alternatively, they may be related to differences in the experimental methodologies employed, as Guiraud et al. (2011) used an oddball ERP paradigm including a stream of standard pure tones, whereas the present experimental design included pairs of social and non-social sounds. Interestingly, the investigation of the relationship between early sensory processing of non-human action sounds and communication and social skills in the current study revealed that the early P1 repetition suppression effect in response to non-human action sounds over the frontal cortex was associated with lower verbal ability scores on the MSEL in the low-risk group. However, the temporal N1 repetition suppression effect was associated with better performance on the ADOS communication subscale in the high-risk group. These results may reflect different language and communication-related functions associated with the P1 and N1 components, which, however, warrant further investigation due to the small sample included in the current study.

Although no significant group differences were found for the early stages of non-human action sound processing, the examination of repetition suppression effects elicited by non-human action sounds within later stages of perceptual processing revealed an additional N4 repetition suppression effect over parietal channels, which was present only in the high-risk group. This finding may reflect enhanced non-social neural processing mechanisms in high-risk toddlers, extending previous ERP findings in 10-month old infant siblings of children with ASD, who were found to process pictures

of objects faster that low-risk controls (McCleery et al., 2009). Similar findings have also been reported by an ERP study in children with ASD, which also revealed larger cortical responses to objects in children with autism compared to typically developing controls (Webb et al., 2006).

The current results of atypical non-human action sound processing are also consistent with the findings from our study of human action sound processing in children with ASD described in Chapter 4, which also revealed greater neural activity elicited by environmental sounds over the parietal cortex in the ASD group compared to both chronological age- and verbal age-matched controls. However, children with ASD also exhibited less habituation to human action sounds within approximately the same stage of perceptual processing. The lack of prominent deficient human action processing mechanisms along with the presence of enhanced non-social processing mechanisms found in high-risk toddlers in the present study may suggest that this aspect of functioning is an endophenotype for ASD. Alternatively, this atypicality may reflect a distinct non-social versus social processing profile in toddlers who are at risk for autism but do not meet behavioural criteria for an ASD. Along these lines, enhanced processing of non-social stimuli may constitute a consequence of increased attention to non-social stimuli in the environment, such as objects or non-speech sounds, previously documented in behavioural research studies of younger high-risk infants (e.g., Curtin & Vouloumanos, 2013; Droucker, Curtin & Vouloumanos, 2013; Noland et al., 2009). Finally, enhanced non-social processing may reflect a compensatory neural processing strategy in high-risk toddlers who are not on the autism spectrum. Interestingly, habituation to non-human action sounds was found to be associated with better performance on the ADOS activities assessing creativity and imagination in the high-

risk group, as well as with better social and communication skills, as measured by the Q-CHAT, in the low-risk group. These findings may reflect a key role that habituation to non-social stimuli, such as object or environmental sounds, may play in the development of creativity and social skills as a part of a perceptual learning process in early childhood. However, they should be viewed with caution due to the large number of factors explored in the current analyses and the relatively small group of participants recruited in the present study.

Study 2

In order to develop a better understanding of social and non-social processing differences between toddlers who may be on the autism spectrum and high-risk toddlers who may share a common ASD-related endophenotype, as well as low-risk typically developing toddlers, an additional group of 2- to 3-year old toddlers with high scores on the ADOS-G was tested. All toddlers included in this additional group met cut-off behavioural criteria for an ASD during the administration of the ADOS-G, and were subsequently referred to external community clinical services for a diagnosis of autism.

The results of this second analysis revealed the same neural time-course for human and non-human action sound processing over frontal and temporal cortices in all comparisons. However, in accordance with the results from the first set of analyses, the comparison between chronological age-matched high-risk and low-risk toddlers revealed the same group differences over the parietal cortex, driven by larger N4 repetition suppression effects in response to non-human action sounds in the high-risk group. On the other hand, no significant differences were found between the high-risk and ASD groups, apart from a trend in the ASD group for faster habituation to

environmental sounds over the left frontal cortex at an early stage of sensory processing. The latter was also found to be associated with higher scores on the MSEL visual reception sub-scale in toddlers with ASD, whereas less habituation to non-human action sounds as reflected in the P1 mean amplitude was found to be associated with higher expressive language scores on the MSEL in the ASD group. On the other hand, with respect to perceptual processing of human and non-human action sounds over posterior sites, both groups showed less habituation to human action sounds as well as enhanced perceptual processing of non-human action sounds within the same time window (N4) over the parietal cortex. In addition, enhanced non-human action sound processing over the parietal channels was associated with lower receptive language scores, whereas increased habituation to human action sounds over frontal sites was observed to be associated with higher verbal age as measured by the MSEL in the ASD group. Taken together, these results provide preliminary evidence for a potential association of social processing with language ability and non-social processing with visual perception skills in the ASD group. Notably, the latter have been found to be developed to a higher level in children with autism (Happe & Frith, 2006). However, the current results need to be explored further in future studies and replicated in larger groups of participants.

On the other hand, the comparison of toddlers with suspected ASD with typically developing low-risk controls revealed slightly different results; no significant repetition suppression effects were found either for human or non-human action sounds at a late stage of perceptual processing over temporal or parietal sites. Instead, a lateralisation difference for human action sounds was revealed between the groups, with the low-risk group showing greater N4 repetition suppression effects over the right frontal cortex,

whereas toddlers with ASD did not show any lateralisation differences, but only a trend for leftward lateralisation. These findings extend previous ERP findings of Orekhova et al. (2009) who presented pairs of non-social sounds (clicks) to young children with ASD and typically developing children, and found ERP lateralisation differences between the groups. Specifically, although the stimulus repetition effects were not significantly different between the groups, typically developing children exhibited greater temporal N1c activity over the right hemisphere in response to the first – contextually and temporary novel- stimuli (presented in pairs). However, ERP responses to the first stimuli in the ASD group were reduced over the right temporal cortex and followed by a leftward lateralisation (Orekhova et al., 2009). Although lateralisation differences in the present study were observed within later stages of perceptual processing in response to stimuli from a novel perceptual category, together these findings provide preliminary evidence for reduced right hemisphere activation in response to temporary or perceptually novel stimuli in children with ASD. In addition, the current data extend recent fNIRS findings of Lloyd-Fox and colleagues (2013), who showed that infants at risk for ASD exhibited atypically right lateralised temporal activity in response to visual social stimuli, in contrast to low-risk infants who showed significant haemodynamic responses over the temporal cortex, and especially over the left hemisphere. Taken together, the Lloyd-Fox et al. (2013) and the current findings may suggest that atypically lateralised cortical responses to auditory social stimuli, such as action-related sounds and non-speech vocalisations, may be part of the ASD endophenotype in infancy and may eventually be more prominent in toddlers developing autism. This hypothesis is also supported by recent fMRI findings revealing weak functional connectivity between the left and right hemisphere in cortical regions

associated with language development in toddlers with ASD, when compared with toddlers with language delays and typically developing toddlers (Dinstein et al., 2011).

Conclusions

The present study is the first to examine the auditory processing of nonverbal human action sounds versus non-human action sounds in high-risk toddler siblings of children with ASD, or toddlers who meet the behavioural criteria for an ASD on the ADOS-G. The present data from the first set of analyses reveal significant non-social processing differences between high-risk and low-risk toddlers, with high-risk toddlers showing enhanced perceptual processing of non-human action sounds. In addition, in the second set of analyses, faster cortical responses to non-human action sounds at an early stage of processing was also found in the ASD group compared to high-risk toddlers, who did not meet cut-off behavioural criteria for an ASD. However, enhanced non-social processing mechanisms at a later stage of cognitive processing were found in both the ASD and high-risk groups. These effects are similar with the enhanced non-social processing effects previously found in 4- to 6-year old children with ASD (see *Chapter 4*) and provide evidence for shared enhanced non-social processing mechanisms in toddlers and children with ASD and high-risk toddler siblings. In addition, they extend previous findings of enhanced visual non-social processing mechanisms observed in high-risk infants and children with ASD (McCleery et al., 2009; Webb et al., 2006).

On the other hand, the comparison between toddlers with ASD and low-risk typically developing toddlers revealed atypically lateralised social processing mechanisms over the frontal sites in the ASD group. These results provide preliminary

evidence for atypical auditory social processing in toddlers with ASD, and extend previous research showing impaired visual processing of human actions in children with ASD (e.g. Oberman et al., 2005; Oberman, Ramachandran and Pineda, 2008). However, the present findings need to be replicated in larger samples, and with the ASD, high-risk, and low-risk participant groups all matched for both chronological and verbal age. For example, the comparison of verbal age-matched ASD and typically developing groups may further our understanding of the nature of the lateralisation differences found between the groups in the current study. In addition, given that autism cannot currently be reliably diagnosed until 3 years of age (e.g., Chawarska et al., 2009; Chawarska et al., 2007; see also McCleery, Stefanidou, & Graham, 2011), the completion of an ADOS-G follow-up assessment at 3 years of age or older with all toddlers in the high-risk and ASD groups, as well as the provision of a community clinical diagnosis to toddlers that obtained high-scores on the ADOS-G, would help to firmly establish the diagnostic status for all participants in both groups.

Despite the aforementioned limitations of the present study, it is important to note that differences in human action- and non-human action-related sound processing observed between the groups may be driven by impairments in social attention or an imbalance between social and non-social attention in high-risk toddlers and toddlers with ASD. Impaired social attention, as well as enhanced non-social attention, have been previously observed in both children and adolescents with ASD, as well as high-risk infant siblings of individuals with ASD (e.g. Curtin & Vouloumanos, 2013; Dawson et al., 1998; Droucker, Curtin & Vouloumanos, 2013; Klin, 1991; Klin et al., 2002a; Kuhl et al., 2005; Mosconi et al., 2009; Noland et al., 2009; Pierce et al., 2011; Shic et al. 2011; Shultz, Klin & Jones, 2011; Zwaigenbaum et al., 2005). According to

Dawson's (2008) *Social Motivation Hypothesis* (see also *Chapters 1 & 4*), social attention is mediated by neural systems, which are responsible for the formation of reward representations in the brain. Consequently, impaired reward processing neural systems in ASD may result in reduced attention and engagement with the social world, which may drive reduced cortical specialisation and deficient social processing brain mechanisms (Dawson, 2008; Nelson, 2001). Therefore, future research should include the investigation of the relationship between cortical responses to auditory social and non-social stimuli and behavioural performance on social attention measures in high-risk toddlers and toddlers with ASD symptoms. In addition, attentional modulation during the EEG/ERP assessments (e.g., Whitehouse & Bishop, 2008) may provide a better understanding of the role of social versus non-social attention in brain activity and in consequent cortical specialisation to visual or auditory social stimuli, such as human action sounds or non-speech vocalisations.

In summary, the current data suggest that toddlers at risk for ASD are characterised by enhanced auditory, non-social early cognitive processing mechanisms, whereas toddlers with suspected ASD present with neural processing atypicalities in their early cognitive cortical responses to auditory social stimuli. These findings provide insight into similarities and differences between the neural underpinnings of early communication and social interaction difficulties observed in high-risk toddlers compared with toddlers who are on the autism spectrum. In addition, they highlight the importance of non-social preferences or attention as a potential strength, and possible compensatory strategy, observed in this high-risk population. Finally, the information generated by the current findings may also contribute to the development of implicit

diagnostic measures or more effective early intervention strategies for toddlers and young children with ASD in the future.

CHAPTER 6:

GENERAL DISCUSSION

6.1 Summary of findings

In the present studies, we utilised event-related potentials in order to investigate the nature, time-course, and neurodevelopmental trajectory of the neural mechanisms of human versus non-human action sound processing in typically developing toddlers and young children, children with autism spectrum disorders, and toddler siblings of children with ASD. In order to do this, we used an auditory-auditory repetition suppression ERP paradigm and examined children's neural responses to repeated (congruent) versus non-repeated (incongruent) human and non-human action sounds. In addition, we used standardized behavioural measures in order to match the comparison groups on verbal abilitiy, and to investigate the relationship between brain activity and social communication and cognitive skills.

The results of the first study in typically developing toddlers and children (see *Chapter 3*) revealed repetition suppression effects to both human and non-human action sounds in both two-year old toddlers and four- to five-year old children. The examination of the time-course of human action sound processing mechanisms revealed both early sensory processing and later perceptual processing ERP components over frontal, temporal, and parietal sites, whereas environmental sounds elicited significant repetition suppression effects only at an early stage of sensory processing over frontal and temporal regions. Although no group differences were observed for non-human action sound processing, the brain mechanisms associated with the perceptual processing of human action sounds over the frontal cortex were found to be right lateralised in two-year old toddlers, whereas four- to five-year old children exhibited bilateral activity.

In the second study (see *Chapter 4*), four- to six-year old high-functioning children with ASD were compared to typically developing children, matched for gender, chronological age, and verbal age. In accordance with the findings reported in the typical development study, the results revealed the same time-course for both human and non-human action sound processing over frontal, temporal, and parietal regions in both the ASD and control groups. However, children with ASD exhibited enhanced cortical responses to non-human action sounds at an early stage of cognitive processing over parietal sites. In addition, they exhibited less habituation to human action sounds at a later stage of perceptual processing over the same region, when compared with typically developing children.

Finally, in the third study (see *Chapter 5*), two- to three-year old toddlers at risk for ASD were compared with low-risk toddlers, matched for gender, and chronological and verbal age. In addition, in a second set of analyses, high-risk toddlers were compared with both toddlers with ASD and low-risk typically developing toddlers, matched for gender and chronological age. The time-course of human and non-human action sound processing mechanisms revealed from these comparisons was similar to the neural processing time-course found in the previous studies. Notably, in accordance with findings in children with ASD, high-risk toddlers presented with enhanced non-social processing mechanisms within the same stage of early cognitive processing over posterior sites, when compared with low-risk controls. In addition, the comparison of high-risk toddlers who did not meet the behavioural criteria for an ASD on the ADOS-G with toddlers with ASD revealed both enhanced perceptual processing of non-human action sounds and apparently reduced habituation to human action sounds. However, no perceptual processing differences were found between the high-risk and ASD groups for

either human or non-human action sounds. Finally, when toddlers with ASD were compared with low-risk typically developing toddlers, they were found to exhibit atypical lateralization for human action sound processing at a late stage of cognitive processing. More specifically, brain mechanisms associated with human action sound processing in low-risk typically developing toddlers were found to be right lateralised, whereas toddlers with ASD showed no lateralisation differences and a trend for a human action sound repetition suppression effect only over the left and middle frontal regions.

The current findings provide evidence for the development of specialised neural mechanisms associated with the perceptual processing of human versus non-human action sounds by two years of age, as well as for the existence of lateralization differences across different age groups in early childhood. More specifically, they extend previous findings revealing the development of distinct neural mechanisms for the visual processing of biological motion or human actions by 8 months of age (e.g. Hirai & Hiraki, 2005; Reid, Belsky & Johnson, 2005). In addition, our results in typically developing toddlers and young children revealed a similar time course for auditory social (human action) and non-social (non-human action) processing mechanisms as the one previously found in adults (Giusti et al., 2010). Taken together, the current ERP findings have shown that auditory social processing mechanisms start to develop by two years of age and are similar to those observed in adults (see Giusti et al., 2010). In addition, the present results in early typical development complement previous auditory human action perceptual processing EEG findings in 8-month old infants (Paulus et al., 2012). However, frontal lateralisation differences between toddlers and young children, observed in the current study, may highlight potential

neurodevelopmental differences in gesture processing and understanding between toddler and child groups, as previously found in behavioural and ERP research studies using visual stimuli in the same age groups (Namy, Campbell, & Tomasello, 2004; Sheehan, Namy, & Mills, 2007).

On the other hand, the present results in young children with autism and toddlers at risk of developing ASD revealed cortical processing similarities between the ASD and high-risk groups, as both groups showed enhanced non-social processing mechanisms, whereas the former also exhibited atypical responses and reduced habituation to human action sounds. These results are consistent with recent behavioural and neuroimaging research findings showing reduced habitutation to other types of visual social stimuli (i.e. faces) in toddlers and adults with autism, respectively (Kleinhans et al., 2009; Webb et al., 2010). They also extend previous EEG and ERP research revealing impaired perceptual processing of visual human action stimuli or biological motion in individuals with ASD (e.g. Bernier et al., 2007; Kroger et al., 2013; Oberman et al., 2005). In addition, the present findings of enhanced non-social processing mechanisms in the ASD and high risk groups complement previous ERP findings showing faster neural responses to visual non-social compared to social stimuli (i.e. pictures of objects versus faces) in young children with ASD (Webb et al., 2006), as well as in high-risk infant siblings of children with ASD (McCleery et al., 2010). Interestingly, enhanced non-social attention or a preference for visual or auditory non-social stimuli have also been documented in several previous research studies in individuals with ASD and high-risk infants, employing either behavioural experimental designs or eye-tracking methodology (e.g. Curtin & Vouloumanos, 2013; Droucker, Curtin, & Vouloumanos, 2013; Klin et al., 2002b; Kuhl et al., 2005; Pierce et al., 2010;

Shultz, Klin, & Jones, 2011). Notably, the current findings revealed enhanced non-social processing mechanisms in both the ASD and the non-ASD high-risk groups on the same auditory perceptual processing ERP paradigm and may, therefore, uncover a shared ASD endophenotype in both groups, complementing the aforementioned ERP findings in the visual modality.

Although our findings in children with ASD were consistent across the two comparisons with chronological age- and verbal age-matched control groups, they were not replicated in 2- to 3-year old toddlers who met behavioural criteria for an ASD on the ADOS-G. Instead, toddlers with ASD showed a lack of lateralization to human action sounds over the frontal region, as opposed to chronological age-matched controls. Similar atypicalities in lateralisation of cortical responses to both auditory social (i.e. non-speech human vocalisations) and non-social stimuli (i.e. clicks) have been previously documented in both infants at risk for autism and young children with ASD, respectively (Lloyd-Fox et al., 2013; Orekhova et al., 2009). It is important to note, however, that, unlike the groups tested in our study in children with ASD (see *Chapter 4*), toddlers with ASD that were included in the additional set of analyses in the latter study (see *Chapter 5*) were not matched to the comparison groups on verbal ability.

In sum, our findings have addressed the aims and hypotheses of the current studies, initially outlined in the introduction of the present thesis. First of all, by using an auditory-auditory repetition suppression ERP paradigm in toddlers and young children, we established the typical developmental trajectory of human and non-human action sound processing mechanisms in two different age groups in early childhood and identified neurodevelopmental differences between toddlers and young children.

Second, by using the same ERP paradigm in young children with ASD, we revealed differences in the development of both auditory social and non-social neural processing mechanisms between the ASD and typically developing groups. Similarly, in our last study, we managed to identify similarities and differences in auditory perceptual processing of social and non-social stimuli (i.e. action and non-action-related sounds) between toddlers at risk of developing autism and low-risk toddlers, as well as between toddlers who met behavioural criteria for an ASD on the ADOS-G and non-ASD high-risk or low-risk toddlers. Finally, we also explored the relationship between cortical responses to both auditory social and non-social stimuli and cognitive or social communication skills, as scored on the standardised behavioural measures employed in the current studies, in all toddler and child groups. However, the results from correlation analyses were viewed with caution due to the small samples recruited in the present studies and the large number of factors explored.

6.2 Limitations

Although the current studies are the first ERP studies to examine the time-course and neurodevelopmental trajectory of human versus non-human action sound processing mechanisms in typically developing young children, children with ASD, and toddlers at risk for ASD, it is important to note a few limitations that should be addressed in future research.

First, with respect to the sample assessed in the first study, presented in *Chapter 3*, a group of typically developing two-year old toddlers (n=24) was compared with a group of typically developing four- to five-year old children (n=24), matched for gender. However, no validated measure of hand preference or handedness was used, and

information related to handedness was based on parents' reports. As a result, hand preference-related information was not available from parents of two-year old toddlers, who did not exhibit a hand preference that was obvious to their parents at the time of the study. Therefore, it is unknown whether right lateralization of human action sound processing mechanisms found in the toddler group is associated with neurodevelopmental changes across the age groups or hand preference. This hypothesis is based on recent findings revealing that some infants develop a hand preference for acquiring objects by 14 months of age, which is stable until two years of age when new skills develop (Nelson, Campbell, & Michel, 2013). In addition, Nelson and colleagues (2013) reported that even infants, who did not show a hand preference, exhibited a preference for right or left hand use by two years of age. Consequently, the use of valid hand preference measures may be necessary for the interpretation of lateralization effects in these young groups in future studies investigating visual or auditory human action or gesture neural processing.

The second study, presented in *Chapter 4* of the current thesis, compared a group of eighteen children with ASD with a group of typically developing children (n=18), matched for gender and chronological age. In addition, in the second set of analyses, only fourteen children were included in each group, in order for them to be matched for verbal age. Although the results were consistent across the two group comparisons, the current findings need to be replicated in larger groups, matched for both chronological and verbal age. In addition, the comparison of groups matched for non-verbal ability and motor skills is also critical, given that previous findings have shown a positive relationship between fine motor skills and visual human motion processing in typically developing infants (Reid, Belsky, & Johnson, 2005). Moreover, due to difficulties in

recruiting female participants with ASD, there was only one female participant in each of the comparison groups. The replication of the present results in female individuals with ASD may help us develop a better understanding of social and non-social processing mechanisms in autism through the assessment of a more representative sample of individuals with ASD, and would allow for the investigation of potential social or non-social processing differences between males and females with ASD. Finally, the confirmation of a formal clinical diagnosis of ASD for all participants who took part in the current study is important for the interpretation of the present findings.

The third study, presented in *Chapter 5* of the current thesis, included two sets of analyses comparing high-risk (*n*=18) with low-risk toddlers (*n*=18), matched for gender, chronological age and verbal ability, as well as high-risk toddlers (*n*=13) with low-risk toddlers (*n*=13) and toddlers who met behavioural criteria for an ASD on the ADOS-G (*n*=13), matched for gender and chronological age. The replication of the current study in larger groups of participants, matched for both chronological and developmental age that would not account for differences in cortical processing between the groups, may reveal distinct auditory social and non-social processing mechanisms associated only with ASD symptoms experienced by the ASD group, as opposed to ASD-related behavioural traits and/or compensatory strategies present only in high-risk toddlers with no ASD diagnosis.

On the other hand, with regards to the methods employed in the current studies, ERPs are among the most established techniques for the study of the neural mechanisms underlying visual or auditory perception, attention and cognition in typical and atypical development in infants and young children, as they are easy to use and provide high temporal resolution (de Haan, 2007; Nelson & McCleery, 2008). However, they are also

characterized by low spatial resolution and, therefore, it is quite difficult to localise the sources of the brain activity recorded over the scalp (Nelson & McCleery, 2008). The use of other brain imaging methods, such as fNIRS and fMRI, may complement the current research findings by providing more information related to the brain regions associated with the neural functions and mechanisms examined in the current studies.

Finally, the methods used here for the completion of the ERP assessments have been previously used by numerous studies examining auditory and speech processing in infants and young children (e.g. Coffey-Corina, Padden, & Kuhl, 2008; Kuhl et al., 2005; Lepisto et al., 2005; Lepisto et al., 2006; Orekhova et al., 2009; Orekhova et al., 2012; Whitehouse & Bishop, 2008), and included the presentation of silent cartoon videos, which included both human and non-human actions. The concurrent presentation of visual stimuli during auditory processing ERP assessments in infants and young children is necessary in order to reduce artifacts in the signal, caused by body or facial movements (Lloyd-Fox et al., 2013). Although none of the visual stimuli included in the videos were associated with any of the auditory stimuli used in the ERP paradigm, and also were not synchronised with them, we can not be certain that the visual stimulation did not affect cortical responses to the auditory social and non-social stimuli. Therefore, it may be useful to employ methods, such as the ones utilised by Lloyd-Fox and colleagues (2013) in their fNIRS study in high-risk and low-risk infants. The authors examined both visual and auditory processing of social videos and vocal versus non-vocal stimuli, respectively, and they used the same social videos during both experiments. This may be an effective method to control for the potential effects of the concurrent visual stimulation on auditory processing. However, it is important to note that it may be easier to associate vocal stimuli, including laughing and crying, with

actors presented in social or cartoon videos. One of the advantages of the present studies is the fact that the auditory human action stimuli presented in the current ERP paradigm included only sounds produced by hand actions, which were not included in any of the videos presented during the ERP assessment.

6.3 Directions for future research

The current ERP data in typically developing toddlers and young children add to a growing body of electrophysiological research that provides evidence for the early development of visual and auditory human action processing mechanisms by two years of age (Marshall, Young, & Meltzoff, 2011; Paulus et al., 2012; Reid, Belsky, & Johnson, 2005; van Elk et al., 2008; Warreyn et al., 2013). Although the present study was the first ERP study to investigate the time-course and neurodevelopmental trajectory of auditory processing of sounds produced by human actions in young children, only two types of human action sound stimuli were used. The use of a larger range of hand or mouth action sound stimuli by future studies (as previously done by Pizzamiglio et al. (2005) in adults) may help us develop a better understanding of human action sound processing mechanisms in young children, as well as examine similarities and/or differences between brain mechanisms underlying the perceptual processing of body actions and speech or non-speech vocalisations. Notably, biological motion and speech perception have been suggested to be mediated by shared neuroanatomical substrates (Redcay, 2007). The investigation of the brain mechanisms associated with both social and speech perception in children with ASD, when compared with both typically developing children and children with language delays,

may further our understanding of the relationship between social communication difficulties and language impairments in autism (see also Redcay, 2007).

Further directions for future research include the use of oddball ERP paradigms including auditory social stimuli, in order to examine habituation effects to human action sounds more thoroughly. Alternatively, the investigation of cortical responses to both the first and second stimuli presented in pairs in RS ERP paradigms would also reveal short-term habituation effects more directly, through the direct comparison of neural responses to the first stimulus with those elicited by the second one. In addition, the use of different stimuli from the same perceptual category in pairs (e.g., two different types of human action sounds) would allow for the examination of repetition suppression effects in response to semantically repeated versus globally repeated pairs. Interestingly, this has been previously examined in neurotypical adults by Giusti and colleagues (2010), who demonstrated that RS effects differed between the two types of stimulus pairs only at an early stage of sensory processing. In contrast, no differences were found between neural responses to semantically and globally repeated pairs at a later stage of perceptual processing. The investigation of RS effects to globally versus semantically repeated pairs of human action sounds in toddlers and children with ASD, and high-risk toddlers, may help us develop a greater understanding of the development of short-term memory and habituation mechanisms for auditory social stimulus processing in ASD. Notably, the latter may also affect social perceptual learning processes and may be associated with generalisation difficulties observed in children with ASD (e.g. Koegel, Kuriakose, Singh, & Koegel, 2012).

Finally, attentional modulation during auditory ERP assessments using social and non-social stimuli, including human action sounds or vocalisations, will extend previous

ERP findings of speech processing, which suggest that children with ASD can show typical responses to repeated speech sounds when they are prompted to allocate attention to them (Whitehouse & Bishop, 2008). Whitehouse & Bishop (2008) suggested that these findings may reflect a top-down attentional inhibition to speech sounds in children with ASD, which may also be associated with communication and social interaction deficits observed in autism. Similarly, the use of eye-tracking or behavioural measures of social versus non-social attention or looking preference (e.g. Dawson et al., 1998; Klin et al., 2002a; Kuhl et al., 2005) along with electrophysiological or neuroimaging techniques may further our understanding of the relationship between social attention and neural mechanisms associated with the perceptual processing of visual or auditory human action stimuli (see also Kuhl et al., 2005).

6.4 Clinical implications - Conclusions

In summary, the findings of the present studies reveal differences in the neurodevelopmental trajectory of brain mechanisms underlying human versus non-human action sound processing between two and four to five years of age. In addition, the current data suggest that young children with ASD experience perceptual processing atypicalities for both human and non-human action sounds, whereas high-risk toddlers mostly present with non-human action sound processing atypicalities. Such perceptual processing impairments or enhancements may underlie the communication and social interaction difficulties experienced by young children with autism or toddlers at risk of developing an ASD. The present findings may contribute to the development of implicit, early diagnostic measures for young children with ASD and toddlers at risk for

ASD, as well as more effective early intervention strategies for young children on the autism spectrum, in the future. For example, Reciprocal Imitation Training (RIT) (Ingersoll, 2010) is a naturalistic imitation intervention for young children with autism, targeting communication and social imitation of a play partner's actions and gestures, which we currently use as part of an intervention study funded by Autistica at the School of Psychology of the University of Birmingham. The aim of the study is the investigation of pre- and post-training ERP activity in response to visual (videos of an actor speaking nursery rhymes versus non-social videos) and auditory (human versus non-human action sounds) social stimuli in children with ASD, as well as their pre- and post-training behavioural performance on standardized behavioural measures of imitation, language ability and social communication skills. The implementation of this intervention study will reveal whether perceptual processing atypicalities found in children with autism prior to the intervention will be reduced after treatment, as well as what their relationship is with social imitation skills, language ability, as well as social and communication difficulties experienced by children with ASD before and after the behavioural training.

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APPENDIX A:

Informed Consent Forms

Appendix A1: Informed consent form for typically developing toddlers and children that took part in Study 1, presented in *Chapter 3*.

University of Birmingham Infant and Child Laboratory Research Study
"Children's Brain Processing of Sounds"

Why is this research study being conducted? What is its purpose?

The purpose of this study is to help us understand how normal children process sounds made by people (e.g., hand clapping) and sounds made by things (e.g., helicopter). Your child's participation in this research will also prepare us to study how children diagnosed with autism and other disorders process sounds made by people and things in the future.

Who is conducting this research study, and where is it being conducted?

Dr. Joseph McCleery, and his students and colleagues, are conducting this study in the University of Birmingham Infant and Child Laboratory.

How are individuals selected for this research study? How many will participate?

You are being asked for your child to participate in this study because she or he is developing normally and is between 2-months and 6-years old. There will be approximately 100 participants in this study.

What do I have to do if I am in this research study?

If you agree to participate in this study, you will be asked to bring your child to our laboratory for approximately 1 hour and the following will happen.

We will measure your child's brain activity using a sensor net that has electrodes sewn into it. The electrodes measure the electricity that your child's brain generates. The electrodes will not hurt. We will place the net on your child's head, and squirt a salt-water solution onto sponges that touch your child's head. The salt-water solution is not toxic or dangerous. Your child will sit next to you or on your lap in a quiet, dimly lit room while she or he watches a silent video while sounds made by people and sounds made by things are played in the background.

Are there any risks associated with participating in this study?

There are no known risks associated with the brainwave recordings. However, your child may not be interested in watching the video and listening to the sounds. Your child also may not like to have people put things on her/his head. You are free to withdraw from the study at any time, including if your child becomes upset or unhappy.

What are the benefits of this research study?

There will not be any benefit to your child from participating in this study. You should know that the EEG procedure is not the same as your child might receive in a hospital, and that the experimenters are not trained to interpret EEGs in the way clinical technicians are. Therefore, we will not have information about any implications of the test for your child's health. The investigators, however, will learn more about how children process sounds made by people and sounds made by objects.

What will happen with the information obtained as part of this research study?

The records of this study will be kept private. Your child's name and the other personal details you provide will be stored. However, research data will only be identified by participant number. Computer files will be stored on password-secured computers in the School of Psychology at the University of Birmingham. Paper copies will be stored in locked filing cabinets in the Infant and Child Laboratory and/or in the office of Dr. McCleery. Only researchers directly involved in this study will have access to the information collected. In any sort of study we might publish, we will not include any information that will make it possible to identify a participant.

Will I receive any payments?

You will be paid £10.00 for your child's participation in this study, to help with the costs of traveling to the laboratory. Your child will also receive a small toy for his/her participation in the study. The researcher will arrange for free parking in front of the laboratory during your visit.

Agreement to Participate

I have been satisfactorily informed of the above-described procedures with its possible risks and benefits. I understand that participation in this study is voluntary. If I refuse to participate or choose to drop out of the study at any time, I understand there will be no penalty, and that this decision will not affect my relationship with the University of Birmingham. I am signing this consent form before participating in any research activities. I give permission for my/my child's participation in this study.

_____	_____
Date	Name of Child
_____	_____
Name of Parent or Guardian	Signature of Parent or Guardian
_____	_____
Name of Researcher / Witness	Signature of Researcher / Witness

Appendix A2: Informed consent form for children with autism spectrum disorders that took part in Study 2, presented in *Chapter 4*.

University of Birmingham Infant and Child Laboratory Research Study
"Children's Brain Processing of Sounds" – Consent for Child with Autism

Why is this research study being conducted? What is its purpose?

The purpose of this study is to help us determine whether or not children diagnosed with autism show the same brain activity as other children do, in response to sounds made by people (e.g., hand clapping) and sounds made by things (e.g., helicopter).

Who is conducting this research study, and where is it being conducted?

Joseph McCleery, PhD, Sissy Stefanidou, MSc, and their colleagues, are conducting this study in the University of Birmingham Infant and Child Laboratory.

How are individuals selected for this research study? How many will participate?

You are being asked to participate because your child is between 3-years and 6-years old and has been diagnosed with Autistic Disorder, Asperger's Syndrome, or Pervasive Developmental Disorder – Not Otherwise Specified (PDD – NOS). There will be approximately 100 participants in this study.

What do I have to do if I am in this research study?

If you agree to participate in this study, you will be asked to bring your child to our laboratory for 2 visits over the course of a five week period and the following will happen:

Electrophysiological assessment (one 1-hour visit): We will measure your child's brain activity using a sensor net that has electrodes sewn into it. The electrodes measure the electricity that your child's brain generates. The electrodes will not hurt. We will place the net on your child's head, and squirt a salt-water solution onto sponges that touch your child's head. The salt-water solution is not toxic or dangerous. Your child will sit next to you or on your lap in a quiet, dimly lit room while she or he watches a silent video while sounds made by people and sounds made by things are played in the background.

Behavioral assessments (one 2-hour visit): We will administer behavioral assessments of your child's developmental and language abilities as well as their communication and social skills. These will be videotaped, so that the experimenter can re-examine the child's responses, and they will include tasks, such as naming objects in pictures, using colored blocks to create patterns, playing with figures, doing imitation tasks and answering simple questions. During your child's behavioral assessment, you will be

also asked to complete a simple, short questionnaire, which includes questions related to your child's social and communication skills.

As part of this project, a video recording and/or photograph will be taken of your child and/or you during your participation in this research project. This is completely voluntary and up to you. In any use of these images, your name will not be identified. You may request to stop taping at any time and review any or all portions. All video recordings are kept on password protected computers and / or in a locked cabinet in the lab, and they are identified by the participants' ID numbers. A separate consent form related to the use of recorded images will be also given to you to sign.

Are there any risks associated with participating in this study?

There are no known risks associated with the brainwave recordings. However, your child may not be interested in watching the video and listening to the sounds or they may get tired or bored during the behavioral assessments. Your child also may not like to have people put things on her/his head. You are free to withdraw from the study at any time, including if your child becomes upset or unhappy.

What are the benefits of this research study?

There may not be any direct benefit to you or your child from participating in this study. You should know that this is a research laboratory and that the researchers are not clinical psychologists. Therefore, we will not be able to provide you with a diagnosis in the case that your child does show signs or symptoms of autism or another disorder based on the results of the assessments. Despite this limitation, at your request, we will provide you with a brief report that includes your child's scores on the assessments and general guidelines for interpreting these scores. You are free to share with clinicians and service providers in an effort to provide them with information that may assist her or him in determining whether or not your child warrants further assessments.

You should know that the EEG procedure is not the same as your child might receive in a hospital, and that the experimenters are not trained to interpret EEGs in the way clinical technicians are. Therefore, we will not have information about any implications of the test for your child's health.

If you are concerned about your child's development, other services are available. These include clinical and educational assessment and treatment services through the National Health Service (NHS). Please remember that we are not a clinic; we are a basic research facility.

Participation in this research is entirely voluntary. You may refuse to participate or withdraw at any time. Also, if we perceive that your child is getting upset, the study may be discontinued.

What will happen with the information obtained as part of this research study?

The records of this study will be kept private. Your child's name and the other personal

details you provide will be stored. However, research data will only be identified by participant number. Computer files will be stored on password-secured computers in the School of Psychology at the University of Birmingham. Paper copies will be stored in locked filing cabinets in the Infant and Child Laboratory and/or in the office of Dr. McCleery. Only researchers directly involved in this study will have access to the information collected. In any sort of study we might publish, we will not include any information that will make it possible to identify a participant. Research data obtained from this study will be held indefinitely for use in potential follow up publications as well as in other associated studies.

Will I receive any payments?

You will be paid **£10.00**for your child's participation in this study, to help with the costs of traveling to the laboratory. Your child will also receive a small toy for his/her participation in the study. The researcher will arrange for free parking in front of the laboratory during your visit.

Agreement to Participate

I have been satisfactorily informed of the above-described procedures with its possible risks and benefits. I understand that participation in this study is voluntary. If I refuse to participate or choose to drop out of the study at any time, I understand there will be no penalty, and that this decision will not affect my relationship with the University of Birmingham. I am signing this consent form before participating in any research activities. I give permission for my/my child's participation in this study.

_____	_____
Date	Name of Child
_____	_____
Name of Parent or Guardian	Signature of Parent or Guardian
_____	_____
Name of Researcher / Witness	Signature of Researcher / Witness

Appendix A3: Informed consent form for typically developing children that took part in Study 2, presented in *Chapter 4*.

University of Birmingham Infant and Child Laboratory Research Study
"Children's Brain Processing of Sounds" – Consent for Control Child

Why is this research study being conducted? What is its purpose?

The purpose of this study is to help us understand how normal children process sounds made by people (e.g., hand clapping) and sounds made by things (e.g., helicopter). Your child will be a control participant for children diagnosed with autism and other developmental disorders.

Who is conducting this research study, and where is it being conducted?

Joseph McCleery, PhD, Sissy Stefanidou, MSc, and their colleagues, are conducting this study in the University of Birmingham Infant and Child Laboratory.

How are individuals selected for this research study? How many will participate?

You are being asked for your child to participate in this study because she or he is developing normally and is between 2-months and 6-years old. There will be approximately 100 participants in this study.

What do I have to do if I am in this research study?

If you agree to participate in this study, you will be asked to bring your child to our laboratory for 2 visits over the course of a five week period and the following will happen:

Electrophysiological assessment (one 1-hour visit): We will measure your child's brain activity using a sensor net that has electrodes sewn into it. The electrodes measure the electricity that your child's brain generates. The electrodes will not hurt. We will place the net on your child's head, and squirt a salt-water solution onto sponges that touch your child's head. The salt-water solution is not toxic or dangerous. Your child will sit next to you or on your lap in a quiet, dimly lit room while she or he watches a silent video while sounds made by people and sounds made by things are played in the background.

Behavioural assessments (one 1-hour visit): We will administer behavioural assessments of your child's developmental and language abilities. These will be videotaped, so that the experimenter can re-examine the child's responses, and they will include tasks, such as naming objects in pictures, using colored blocks to create patterns and answering simple questions. During your child's behavioral assessment, you will be also asked to complete a simple, short questionnaire, which will be related to your

child's social and communication skills.

As part of this project, a video recording and/or photograph will be taken of your child and/or you during your participation in this research project. This is completely voluntary and up to you. In any use of these images, your name will not be identified. You may request to stop taping at any time and review any or all portions. All video recordings are kept on password protected computers and / or in a locked cabinet in the lab, and they are identified by the participants' ID numbers. A separate consent form related to the use of recorded images will be also given to you to sign.

Are there any risks associated with participating in this study?

There are no known risks associated with the brainwave recordings. However, your child may not be interested in watching the video and listening to the sounds or they may get tired or bored during the behavioral assessments. Your child also may not like to have people put things on her/his head. You are free to withdraw from the study at any time, including if your child becomes upset or unhappy.

What are the benefits of this research study?

There will not be any benefit to your child from participating in this study. You should know that the EEG procedure is not the same as your child might receive in a hospital, and that the experimenters are not trained to interpret EEGs in the way clinical technicians are. Therefore, we will not have information about any implications of the test for your child's health. The investigators, however, will learn more about how children process sounds made by people and sounds made by objects.

What will happen with the information obtained as part of this research study?

The records of this study will be kept private. Your child's name and the other personal details you provide will be stored. However, research data will only be identified by participant number. Computer files will be stored on password-secured computers in the School of Psychology at the University of Birmingham. Paper copies will be stored in locked filing cabinets in the Infant and Child Laboratory and/or in the office of Dr. McCleery. Only researchers directly involved in this study will have access to the information collected. In any sort of study we might publish, we will not include any information that will make it possible to identify a participant. Research data obtained from this study will be held indefinitely for use in potential follow up publications as well as in other associated studies.

Will I receive any payments?

You will be paid **£10.00**for your child's participation in this study, to help with the costs of traveling to the laboratory. Your child will also receive a small toy for his/her participation in the study. The researcher will arrange for free parking in front of the laboratory during your visit.

Agreement to Participate

I have been satisfactorily informed of the above-described procedures with its possible risks and benefits. I understand that participation in this study is voluntary. If I refuse to participate or choose to drop out of the study at any time, I understand there will be no penalty, and that this decision will not affect my relationship with the University of Birmingham. I am signing this consent form before participating in any research activities. I give permission for my/my child's participation in this study.

_____	_____
Date	Name of Child
_____	_____
Name of Parent or Guardian	Signature of Parent or Guardian
_____	_____
Name of Researcher / Witness	Signature of Researcher / Witness

Appendix A4: Informed consent form for high-risk toddlers that took part in Study 3, presented in *Chapter 5*.

University of Birmingham Infant and Child Laboratory Research Study
"Toddler's Brain Processing of Sounds" – Toddler with Sibling with Autism

Why is this research study being conducted? What is its purpose?

The purpose of this study is to help us find out more about brain responses to sounds made by people (e.g., hand clapping) and sounds made by things (e.g., helicopter sounds) in toddlers who are at increased risk for developing autism.

Who is conducting this research study, and where is it being conducted?

Joseph McCleery, PhD, Sissy Stefanidou, MSc, and their colleagues, are conducting this study in the University of Birmingham Infant and Child Laboratory.

How are individuals selected for this research study? How many will participate?

You are being asked to participate because your toddler has an older sibling with an Autism Spectrum Disorder. There will be approximately 200 participants in this study.

What do I have to do if I am in this research study?

If you agree to participate in this study, you will be asked to bring your child to our laboratory for 2 or 3 visits over the course of a five week period and the following will happen:

EEG Assessment (one 1-hour visit): We will measure your child's brain activity using a sensor net that has electrodes sewn into it. The electrodes measure the electricity that your child's brain generates. The electrodes will not hurt. We will place the net on your child's head, and squirt a salt-water solution onto sponges that touch your child's head. The salt-water solution is not toxic or dangerous. Your child will sit next to you or on your lap in a quiet, dimly lit room while she or he watches a silent video while sounds made by people and sounds made by things are played in the background. The session may be videotaped so that we have a record of your child's activity during the EEG recording.

Behavioral Assessments (one 2-hour visit): We will administer behavioral assessments of your child's developmental and language abilities, as well as her/his communication and social skills. These will include the Mullen Scales of Early Learning, which measures cognitive/motor developmental level in five areas: gross motor, fine motor, visual reception, receptive language, and expressive language. We will also administer the Autism Diagnostic Observation Schedule (ADOS), which measures your child's social and communication skills. Finally, we may administer the Preschool Language Scales, which measures your child's language understanding and production. These

behavioural assessments may be videotaped in order to have a record of your child's behaviour during the testing.

Questionnaires: You will be asked to fill out questionnaires designed to give us information about your biological history, your child, and your family. These may include questionnaires about your toddler's language development, about your toddler's ability to cope with environmental changes, about your older child's social and communication skills, and about your toddler's medical and family history.

As part of this project, a video recording and/or photograph will be taken of your child and/or you during your participation in this research project. This is completely voluntary and up to you. In any use of these images, your name will not be identified. You may request to stop taping at any time and review any or all portions. All video recordings are kept on password protected computers and / or in a locked cabinet in the lab, and they are identified by the participants' ID numbers. A separate consent form related to the use of recorded images will be also given to you to sign.

Are there any risks associated with participating in this study?

There are no known risks associated with the brainwave recordings. However, your child may not be interested in watching the video and listening to the sounds during the EEG assessment. Your child also may not like to have people put things on her/his head. You are free to withdraw from the study at any time, including if your child becomes upset or unhappy.

What are the benefits of this research study?

There may not be any direct benefit to you or your child from participating in this study. You should know that this is a research laboratory and that the researchers are not clinical psychologists. Therefore, we will not be able to rule out a diagnosis of an autism spectrum disorder, or to provide you with a diagnosis in the case that your child does show signs or symptoms of autism or another disorder based on the results of the assessments. You should also know that some children with autism spectrum disorders do not show signs of the disorder until three years of age. Despite these limitations, at your request, we will provide you with a brief report that includes your child's scores on the assessments and general guidelines for interpreting these scores. You are free to share with clinicians and service providers in an effort to provide them with information that may assist her or him in determining whether or not your child warrants further assessments.

You should know that the EEG procedure is not the same as your child might receive in a hospital, and that the experimenters are not trained to interpret EEGs in the way clinical technicians are. Therefore, we will not have information about any implications of the test for your child's health.
If you are concerned about your child's development, other services are available. These include clinical and educational assessment and treatment services through the National Health Service (NHS). Please remember that we are not a clinic; we are a basic research facility.

Participation in this research is entirely voluntary. You may refuse to participate or withdraw at any time. Also, if we perceive that your child is getting upset, the study may be discontinued.

What will happen with the information obtained as part of this research study?

The records of this study will be kept private. Your child's name and the other personal details you provide will be stored. However, research data will only be identified by participant number. Computer files will be stored on password-secured computers in the School of Psychology at the University of Birmingham. Paper copies will be stored in locked filing cabinets in the Infant and Child Laboratory and/or in the office of Dr. McCleery. Only researchers directly involved in this study will have access to the information collected. In any sort of study we might publish, we will not include any information that will make it possible to identify a participant. Research data obtained from this study will be held indefinitely for use in potential follow up publications involving the data as well as in other associated studies.

Will I receive any payments?

You will be paid £10.00 per visit for your child's participation in this study, to help with the costs of traveling to the laboratory. The researcher will arrange for free parking in front of the laboratory during your visit. If you live further than a 1.5 hour commute by train or car, we may also arrange for an overnight stay in a hotel free of charge. Your child will also receive a small toy for his/her participation in the study.

Agreement to Participate

I have been satisfactorily informed of the above-described procedures with its possible risks and benefits. I understand that participation in this study is voluntary. If I refuse to participate or choose to drop out of the study at any time, I understand there will be no penalty, and that this decision will not affect my relationship with the University of Birmingham. I am signing this consent form before participating in any research activities. I give permission for my/my child's participation in this study.

_____	_____
Date	Name of Child
_____	_____
Name of Parent or Guardian	Signature of Parent or Guardian
_____	_____
Name of Researcher / Witness	Signature of Researcher / Witness

Appendix 5: Informed consent form for toddlers diagnosed with autism or suspected autism that took part in Study 3, presented in Chapter 5. Toddlers with autism completed the current ERP and behavioural assessments, as a part of our on-going intervention study, described below.

University of Birmingham Infant and Child Laboratory Research Study
"Effects of Imitation Training on Brain Activity in Children with Autism or Suspected Autism"

Why is this research study being conducted? What is its purpose?

The purpose of this study is to determine whether or not gesture imitation training has an effect on the brain activity of young children with autism as they process videos and sounds made by people (e.g., hand clapping) versus videos and sounds made by things (e.g., helicopter). We will also measure the children's imitation skills and other abilities.

Who is conducting this research study, and where is it being conducted?

Joseph McCleery, PhD, Sissy Stefanidou, MSc, and their colleagues, are conducting this study in the University of Birmingham Infant and Child Laboratory.

How are individuals selected for this research study? How many will participate?

You are being asked to participate because your child is between the ages of 2- and 5-years and has been diagnosed with Autistic Disorder, Asperger's Syndrome, or Pervasive Developmental Disorder – Not Otherwise Specified (PDD – NOS), or is currently being evaluated for one of these disorders or syndromes. There will be approximately 30 participants in this study.

What do I have to do if I am in this research study?

If you agree to participate in this study, you will be asked to bring your child to our laboratory approximately 2 times per week for approximately 14 weeks, and the following will happen:

Pre-Training Assessment Visits (3 Visits, 1.5 Weeks):
Behavioral assessments (two 1.5-hour visits): We will administer behavioural assessments of your child's developmental and language abilities, his/her communication and social skills, as well as his/her imitation skills. . These will include the Mullen Scales of Early Learning, which measures cognitive/motor developmental

level in five areas: gross motor, fine motor, visual reception, receptive language, and expressive language. We will also administer the Autism Diagnostic Observation Schedule (ADOS), which measures your child's social and communication skills. Finally, we will administer two brief assessments of your child's imitation skills. During your child's behavioural assessments, you will be also asked to complete simple, short questionnaires that include questions related to your child's social and communication skills.

Electrophysiological Assessments (one 1-hour visit): We will measure your child's brain activity using a sensor net that has electrodes sewn into it. The electrodes measure the electricity that your child's brain generates. The electrodes will not hurt. We will place the net on your child's head, and squirt a salt-water solution onto sponges that touch your child's head. The salt-water solution is not toxic or dangerous. Your child will sit next to you or on your lap in a quiet, dimly lit room while she or he watches a silent video while sounds made by people and sounds made by things are played in the background. We will also show your child short videos of people talking to him or her, and of things moving around and making bouncing and other sounds.

Training Visits (20 Visits, 10 to 12 Weeks):
Imitation Training: You will be asked to bring your child to our laboratory for two to three 1-hour visits per week and your child will be filmed interacting with an experimenter for 20-minutes across three sessions (1 hour in total per visit). Your child's participation in the training will take between approximately 10 and 12 weeks.

Post-Training Assessment Visits (1 Visits):
Electrophysiological and Behavioural Assessments: After the training is completed, you will be asked to bring your child to the laboratory for one 2-hour visit, in order to complete the post-training EEG assessments (1 hour) as well as the brief behavioural assessments of imitation skills. These are the same assessments described above.

As part of this project, video recordings and/or photographs will be taken of your child and/or you during your participation in the research. This is completely voluntary and up to you. In any use of these images, your name will not be identified. You may request to stop taping at any time and review any or all portions. All video recordings are kept on password protected computers and / or in a locked cabinet in the lab, and they are identified by the participants' ID numbers. A separate consent form related to the use of recorded images will be also given to you to sign. You may request to have your child's data and/or video recordings removed from the study at any time.

Are there any risks associated with participating in this study?

There are no known risks associated with the brainwave recordings. However, your child may not be interested in watching the video and listening to the sounds or they may get tired or bored during the behavioural assessments. Your child also may not like to have people put things on her/his head. You are free to withdraw from the study at any time, including if your child becomes upset or unhappy.

Your child may also become bored during one or more of the training sessions. The training sessions also sometimes involve the experimenter gently physically prompting your child to imitate her or his actions, which may result in mild frustration in some children. The experiments are aware of this, and they will use positive behaviour management procedures in an effort to reduce any frustration that your child may experience. You are encouraged to communicate with the experimenters, including Dr. McCleery, at any time during or after your participation about these things. You are also free to withdraw from the study at any time, including if your child becomes upset or unhappy.

What are the benefits of this research study?

There may not be any direct benefit to you or your child from participating in this study. Although previous research suggests that the training procedures utilised in this study is effective for teaching some children new imitation skills, you should know that not all children learn new skills as a result of the training procedures.

You should also know that this is a research laboratory and that the researchers are not clinical psychologists. Therefore, we will not be able to provide you with a diagnosis in the case that your child does show signs or symptoms of autism or another disorder based on the results of the assessments. Despite this limitation, at your request, we will provide you with a brief report that includes your child's scores on the assessments and general guidelines for interpreting these scores. You are free to share with clinicians and service providers in an effort to provide them with information that may assist her or him in determining whether or not your child warrants further assessments.

You should know that the EEG procedure is not the same as your child might receive in a hospital, and that the experimenters are not trained to interpret EEGs in the way clinical technicians are. Therefore, we will not have information about any implications of the test for your child's health.

If you are concerned about your child's development, other services are available. These include clinical and educational assessment and treatment services through the National Health Service (NHS). Please remember that we are not a clinic; we are a basic research facility.

Participation in this research is entirely voluntary. You may refuse to participate or withdraw at any time. Also, if we perceive that your child is getting upset, the study may be discontinued.

What will happen with the information obtained as part of this research study?

The records of this study will be kept private. Your child's name and the other personal details you provide will be stored. However, research data will only be identified by participant number. Computer files will be stored on password-secured computers in the School of Psychology at the University of Birmingham. Paper copies as well as

copies of videotaped assessment and training sessions will be stored in locked filing cabinets in the Infant and Child Laboratory and/or in the office of Dr. McCleery. Only researchers directly involved in this study will have access to the information collected. In any sort of study we might publish, we will not include any information that will make it possible to identify a participant. Research data obtained from this study will be held indefinitely for use in potential follow up publications as well as in other associated studies.

Will I receive any payments?

You will be paid **£8.00 per visit for each of the visits** for your child's participation in this study, to help with the costs of travelling to the laboratory. These £8.00 payments will be provided to you each time you visit the laboratory. The researcher will arrange for free parking in front of the laboratory during your visit. Your child will also receive a small toy for his/her participation in the study.

Agreement to Participate

I have been satisfactorily informed of the above-described procedures with its possible risks and benefits. I understand that participation in this study is voluntary. If I refuse to participate or choose to drop out of the study at any time, I understand there will be no penalty, and that this decision will not affect my relationship with the University of Birmingham. I am signing this consent form before participating in any research activities. I give permission for my/my child's participation in this study.

_____	_____
Date	Name of Child
_____	_____
Name of Parent or Guardian	Signature of Parent or Guardian
_____	_____
Name of Researcher / Witness	Signature of Researcher / Witness

Appendix A6: Informed consent form for low-risk, typically developing toddlers that took part in the Study 3, presented in *Chapter 5*.

University of Birmingham Infant and Child Laboratory Research Study
"Toddler's Brain Processing of Sounds" – Control Toddler

Why is this research study being conducted? What is its purpose?

The purpose of this study is to help us find out more about brain responses to sounds made by people (e.g., hand clapping) and sounds made by things (e.g., helicopter sounds) in normally developing toddlers and in toddlers who are at increased risk for developing autism.

Who is conducting this research study, and where is it being conducted?

Joseph McCleery, PhD, Sissy Stefanidou, MSc, and their colleagues, are conducting this study in the University of Birmingham Infant and Child Laboratory.

How are individuals selected for this research study? How many will participate?

You are being asked to participate because your toddler's data will serve as control data for another toddler who has an older sibling with an Autism Spectrum Disorder. There will be approximately 200 participants in this study.

What do I have to do if I am in this research study?

If you agree to participate in this study, you will be asked to bring your child to our laboratory for 2 visits over the course of a five week period and the following will happen:

EEG Assessment (one 60-minute visit): We will measure your child's brain activity using a sensor net that has electrodes sewn into it. The electrodes measure the electricity that your child's brain generates. The electrodes will not hurt. We will place the net on your child's head, and squirt a salt-water solution onto sponges that touch your child's head. The salt-water solution is not toxic or dangerous. Your child will sit next to you or on your lap in a quiet, dimly lit room while she or he watches a silent video while sounds made by people and sounds made by things are played in the background. The session may be videotaped so that we have a record of your child's activity during the EEG recording.

Behavioral Assessments (one 90-minute visit): We will administer behavioural assessments of your child's developmental and language abilities. These will include the Mullen Scales of Early Learning, which measures cognitive/motor developmental level in five areas: gross motor, fine motor, visual reception, receptive language, and expressive language. We may also administer the Preschool Language Scales, which measures your child's language understanding and production. These behavioural

assessments may be videotaped in order to have a record of your child's behaviour during the testing.

Questionnaires: You will be asked to fill out questionnaires designed to give us information about your biological history, your child, and your family. These may include questionnaires about your toddler's language development, social development, his or her ability to cope with environmental changes, and about his or her medical and family history.

As part of this project, a video recording and/or photograph will be taken of your child and/or you during your participation in this research project. This is completely voluntary and up to you. In any use of these images, your name will not be identified. You may request to stop taping at any time and review any or all portions. All video recordings are kept on password protected computers and / or in a locked cabinet in the lab, and they are identified by the participants' ID numbers. A separate consent form related to the use of recorded images will be also given to you to sign.

Are there any risks associated with participating in this study?

There are no known risks associated with the brainwave recordings. However, your child may not be interested in watching the video and listening to the sounds during the EEG assessment. Your child also may not like to have people put things on her/his head. You are free to withdraw from the study at any time, including if your child becomes upset or unhappy.

What are the benefits of this research study?

There will not be any direct benefit to you or your child from participating in this study. You should know that this is a research laboratory and that the researchers are not clinical psychologists. Therefore, we will not be able to rule out a diagnosis of an autism spectrum disorder, or to provide you with a diagnosis in the unlikely case that your child does show signs or symptoms of such autism or another disorder based on the results of the assessments. You should also know that some children with autism spectrum disorders do not show signs of the disorder until three years of age. Despite these limitations, at your request, we will provide you with a brief report that includes your child's scores on the assessments and general guidelines for interpreting these scores. You are free to share with clinicians and service providers in an effort to provide them with information that may assist her or him in determining whether or not your child warrants further assessments.

You should know that the EEG procedure is not the same as your child might receive in a hospital, and that the experimenters are not trained to interpret EEGs in the way clinical technicians are. Therefore, we will not have information about any implications of the test for your child's health.

If you are concerned about your child's development, other services are available. These include clinical and educational assessment and treatment services through the National Health Service (NHS). Please remember that we are not a clinic; we are a

basic research facility.

Participation in this research is entirely voluntary. You may refuse to participate or withdraw at any time. Also, if we perceive that your child is getting upset, the study may be discontinued.

What will happen with the information obtained as part of this research study?

The records of this study will be kept private. Your child's name and the other personal details you provide will be stored. However, research data will only be identified by participant number. Computer files will be stored on password-secured computers in the School of Psychology at the University of Birmingham. Paper copies will be stored in locked filing cabinets in the Infant and Child Laboratory and/or in the office of Dr. McCleery. Only researchers directly involved in this study will have access to the information collected. In any sort of study we might publish, we will not include any information that will make it possible to identify a participant. Research data obtained from this study will be held indefinitely for use in potential follow up publications as well as in other associated studies.

Will I receive any payments?

You will be paid £10.00 per visit for your child's participation in this study, to help with the costs of traveling to the laboratory. The researcher will arrange for free parking in front of the laboratory during your visit. Your child will also receive a small toy for his/her participation in the study.

Agreement to Participate

I have been satisfactorily informed of the above-described procedures with its possible risks and benefits. I understand that participation in this study is voluntary. If I refuse to participate or choose to drop out of the study at any time, I understand there will be no penalty, and that this decision will not affect my relationship with the University of Birmingham. I am signing this consent form before participating in any research activities. I give permission for my/my child's participation in this study.

_____	_____
Date	Name of Child
_____	_____
Name of Parent or Guardian	Signature of Parent or Guardian
_____	_____
Name of Researcher / Witness	Signature of Researcher / Witness

APPENDIX B:

Questionnaires for Parents

Appendix B1: Questionnaire for parents of typically developing toddlers and children.

Questionnaire for parents I.D. _____ (for office use)

Thank you very much for agreeing to take part in our study in the Infant and Child Laboratory. We would appreciate if you could complete the following questions carefully. Your answers are strictly confidential, so please be completely honest in responding.

1. Please indicate your child's day, month and year of birth?_____
2. Please indicate the gender of your child: male ☐ female ☐
3. Did you experience any birth complications?

   _____

   _____
4. Has your child experienced any medical problems?

   _____

   _____
5. Has your child experienced any developmental delays? (physical or neurological)

   _____

   _____
6. Has your child experienced any primary sensory impairments (e.g. hearing problems)

   _____

   _____

7. Is there any history of developmental (e.g.Autism), neurological (e.g. epilepsy) or severe psychiatric (e.g. schizophrenia) disorders in your family?

Yes ☐ No ☐

If yes, please indicate:

_____

8. Is your child taking any medication? (please tick)

Yes ☐ No ☐

If yes, please indicate:

_____

9. Is your child bilingual? (please tick) Yes ☐ No ☐

Appendix B2: Questionnaire for parents of children with autism.

Questionnaire for parents I.D. _____ (for office use)

Thank you very much for agreeing to take part in our study in the Infant and Child Laboratory. We would appreciate if you could complete the following questions carefully. Your answers are strictly confidential, so please be honest in responding.

1. Please indicate your child's day, month and year of birth? _____

2. Please indicate the gender of your child: male ☐ female ☐

3. Did you experience any birth complications?

   _____

   _____

4. Please indicate your child's formal diagnosis:

   Autistic Disorder ☐ Asperger's Disorder ☐

   Pervasive Developmental Disorder - Not Otherwise Specified ☐

   If other, please indicate:

   _____

5. Has your child experienced any other neurological problems (e.g. epilepsy)?

   Yes ☐ No ☐

   If yes, please indicate:

   _____

6. Has your child experienced any medical problems?

_____

_____

7. Has your child experienced any primary sensory impairments (e.g. hearing problems)

_____

_____

8. Is your child taking any medication? (please tick)

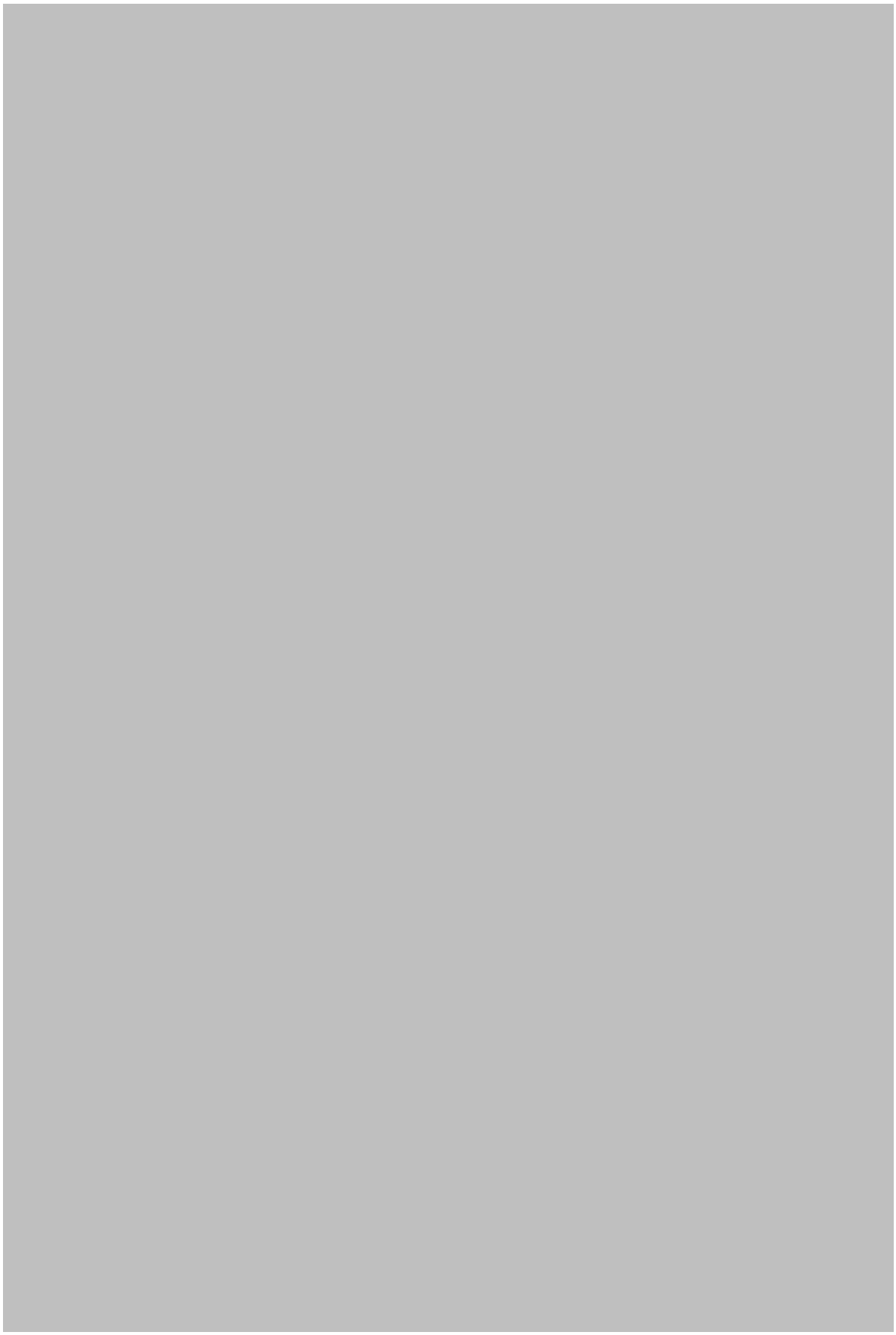
Yes ☐ No ☐

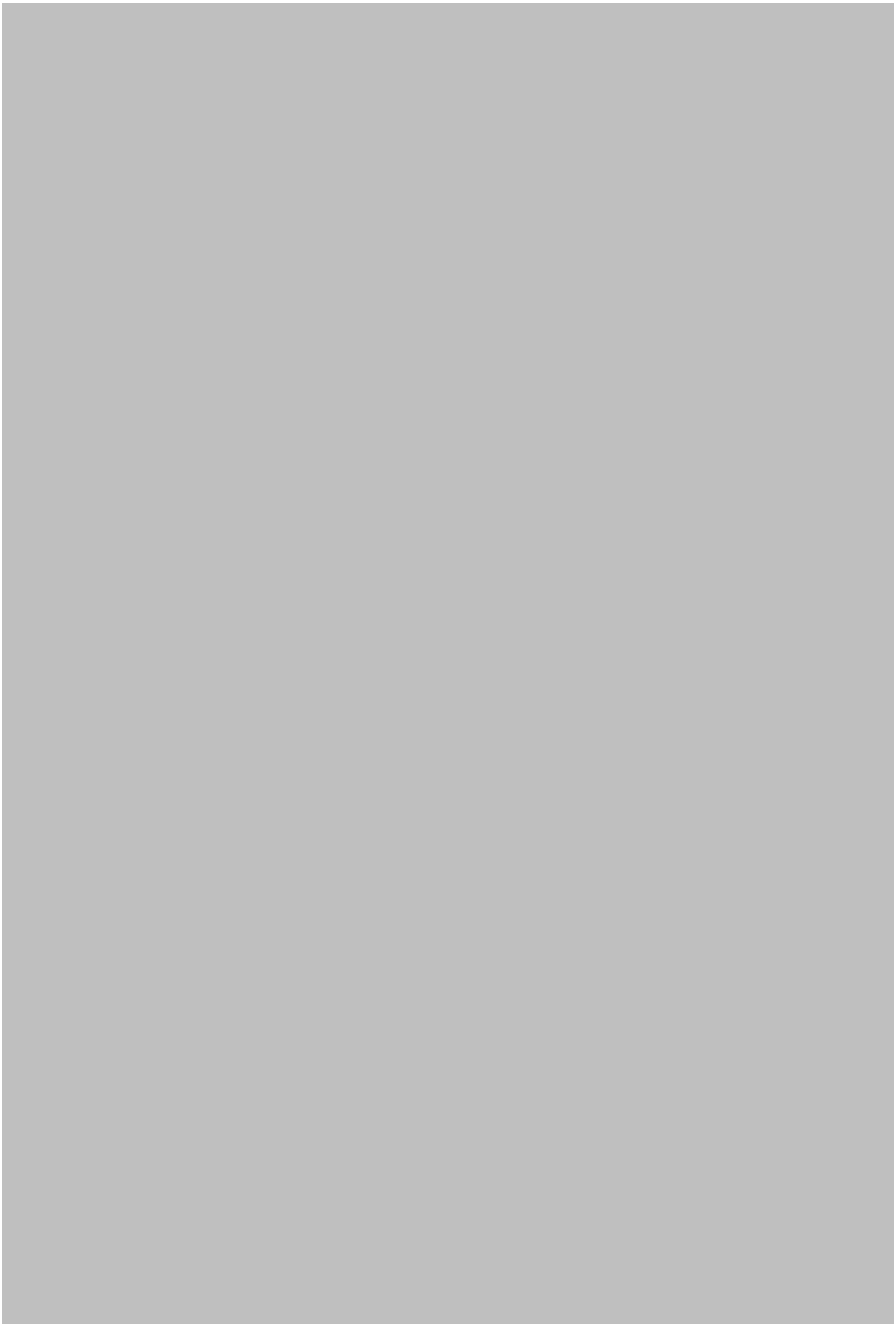
If yes, please indicate:

_____

9. Is your child bilingual? (please tick) Yes ☐ No ☐

Appendix B3: Social Communication Questionnaire –Lifetime (SCQ)





Appendix B4: Quantitative Checklist for Autism in Toddlers (Q-CHAT).

Please answer the following questions about your child by ticking the appropriate circle.
Try to answer EVERY question if you can.

1. Does your child look at you when you call his/her name?

- ○ always
- ○ usually
- ○ sometimes
- ○ rarely
- ○ never

2. How easy is it for you to get eye contact with your child?

- ○ very easy
- ○ quite easy
- ○ quite difficult
- ○ very difficult
- ○ impossible

3. When your child is playing alone, does s/he line objects up?

- ○ always
- ○ usually
- ○ sometimes
- ○ rarely
- ○ never

4. Can other people easily understand your child's speech?

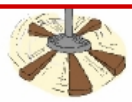
- ○ always
- ○ usually
- ○ sometimes
- ○ rarely
- ○ never
- ○ my child does not speak

5. Does your child point to indicate that s/he wants something (e.g. a toy that is out of reach)?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

6. Does your child point to share interest with you (e.g. pointing at an interesting sight)?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never



7. How long can your child's interest be maintained by a spinning object (e.g. washing machine, electric fan, toy car wheels)?

- ○ several hours
- ○ half an hour
- ○ ten minutes
- ○ a couple of minutes
- ○ less than a minute

8. How many words can your child say?

- ○ none—s/he has not started speaking yet
- ○ less than 10 words
- ○ 10–50 words
- ○ 51–100 words
- ○ over 100 words

9. Does your child pretend (e.g. care for dolls, talk on a toy phone)?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

10. Does your child follow where you're looking?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

11. How often does your child sniff or lick unusual objects?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

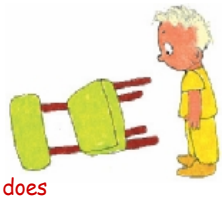
12. Does your child place your hand on an object when s/he wants you to use it (e.g. on a door handle when s/he wants you to open the door, on a toy when s/he wants you to activate it)?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

13. Does your child walk on tiptoe?

- ○ always
- ○ usually
- ○ sometimes
- ○ rarely
- ○ never

14. How easy is it for your child to adapt when his/her routine changes or when things are out of their usual place?



- ○ very easy
- ○ quite easy
- ○ quite difficult
- ○ very difficult
- ○ impossible

15. If you or someone else in the family is visibly upset, does your child show signs of wanting to comfort them (e.g. stroking their hair, hugging them)?

- ○ always
- ○ usually
- ○ sometimes
- ○ rarely
- ○ never

16. Does your child do the same thing over and over again (e.g. running the tap, turning the light switch on and off, opening and closing doors)?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

17. Would you describe your child's first words as:

- ○ very typical
- ○ quite typical
- ○ slightly unusual
- ○ very unusual
- ○ my child doesn't speak

18. Does your child echo things s/he hears (e.g. things that you say, lines from songs or movies, sounds)?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

19. Does your child use simple gestures (e.g. wave goodbye)?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

20. Does your child make unusual finger movements near his/her eyes?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

21. Does your child spontaneously look at your face to check your reaction when faced with something unfamiliar?

- ○ always
- ○ usually
- ○ sometimes
- ○ rarely
- ○ never

22. How long can your child's interest be maintained by just one or two objects?

- ○ most of the day
- ○ several hours
- ○ half an hour
- ○ ten minutes
- ○ a couple of minutes

23. Does your child twiddle objects repetitively (e.g. pieces of string)?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

24. Does your child seem oversensitive to noise?

- ○ always
- ○ usually
- ○ sometimes
- ○ rarely
- ○ never

25. Does your child stare at nothing with no apparent purpose?

- ○ many times a day
- ○ a few times a day
- ○ a few times a week
- ○ less than once a week
- ○ never

APPENDIX C:

Publications

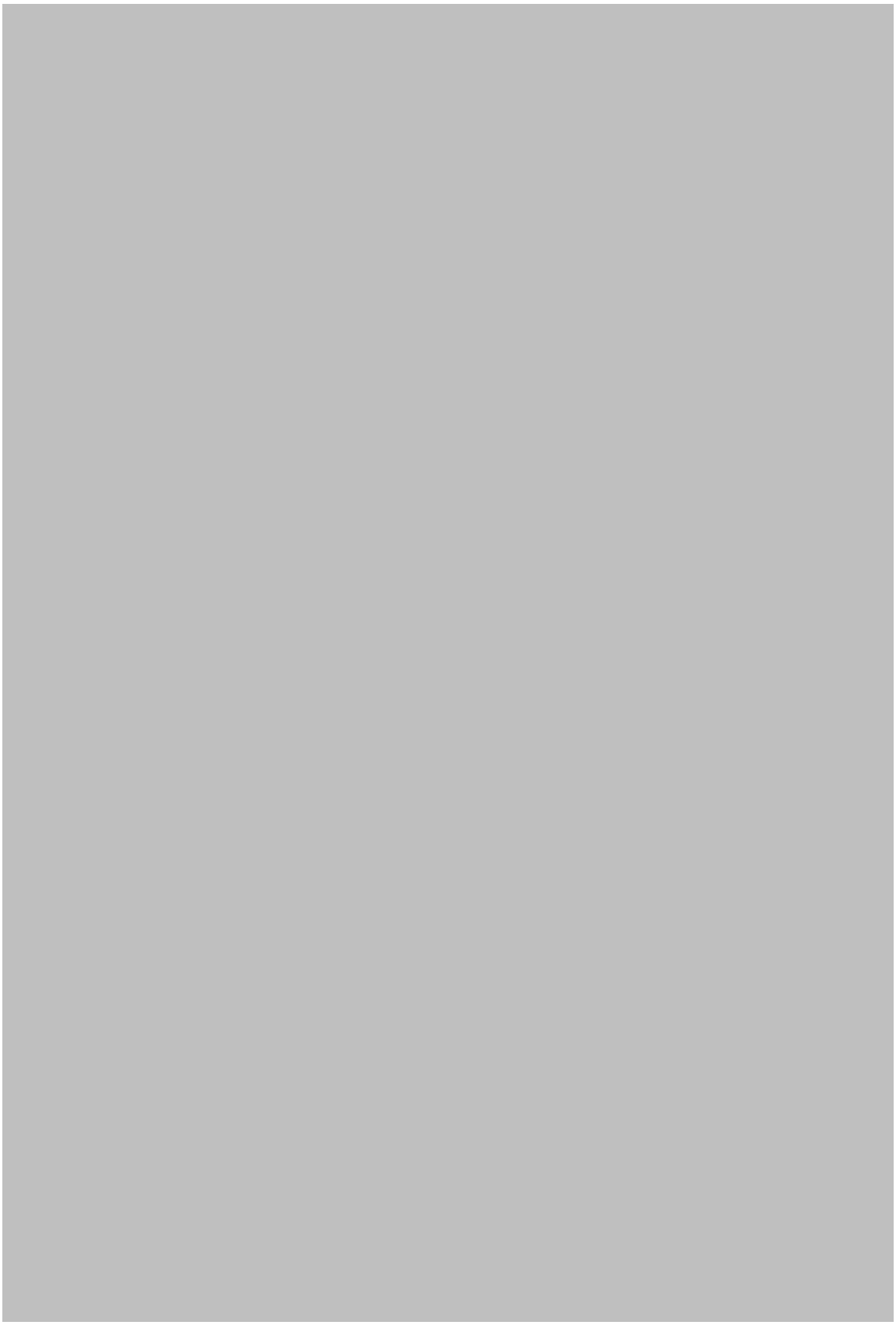
Appendix C1

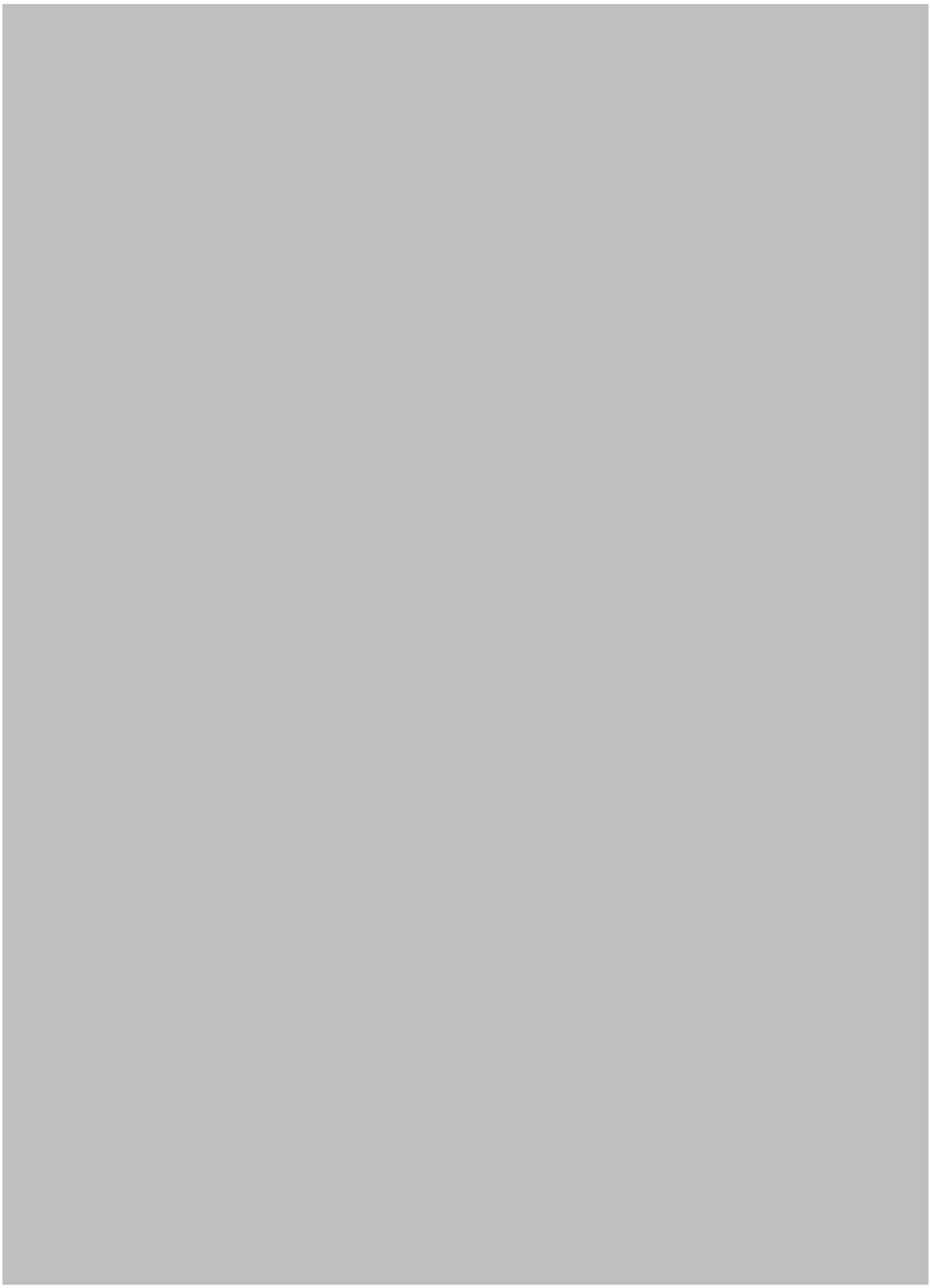
McCleery, J. P., Stefanidou, C., & Graham, K. A. (2011). Neurodevelopment of social/non-social functioning differences in autism. *CARLS Series of Advanced Study of Logic and Sensibility, Volume 5*. Tokyo: Keio University Press.

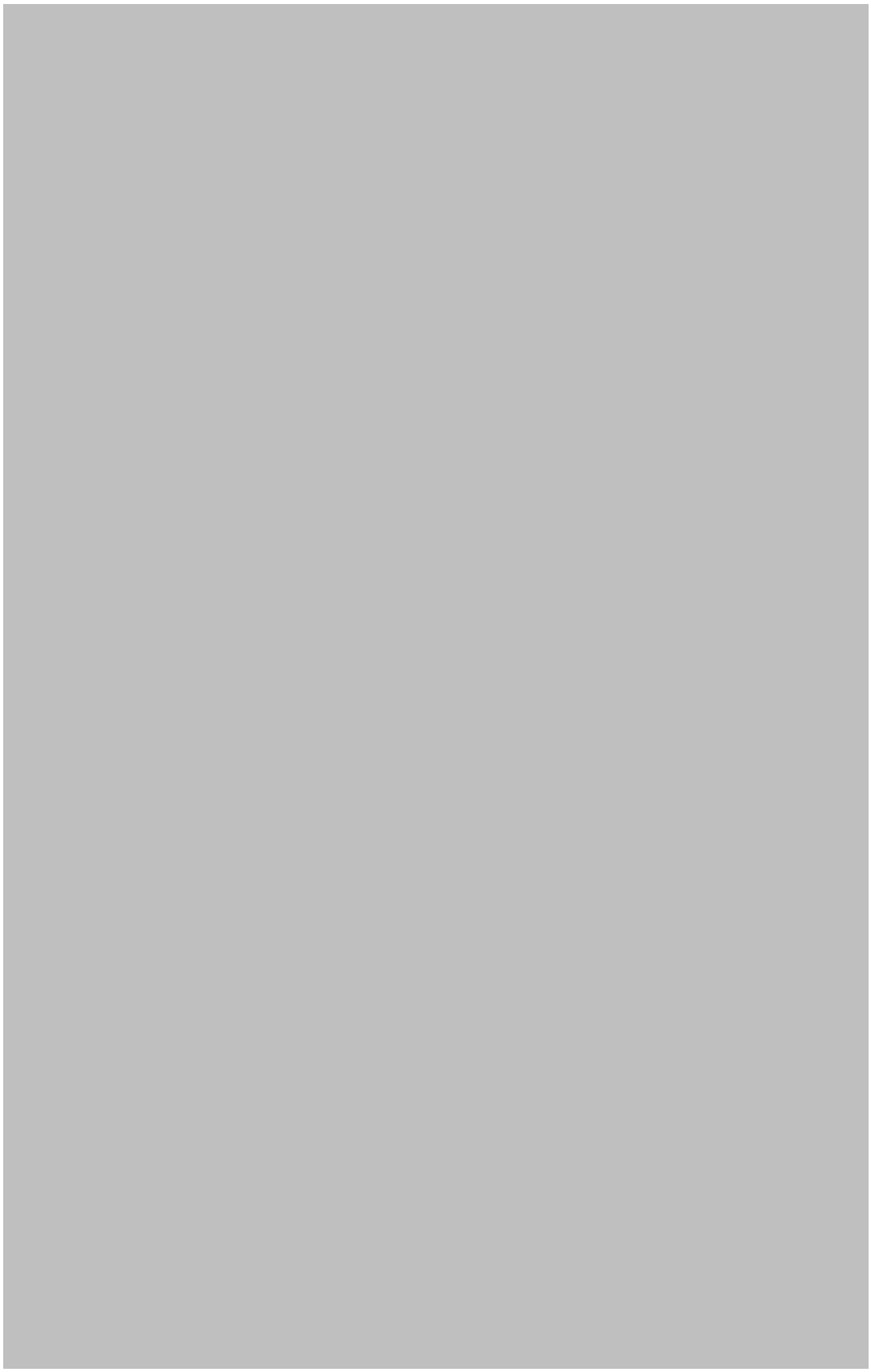
Appendix C2

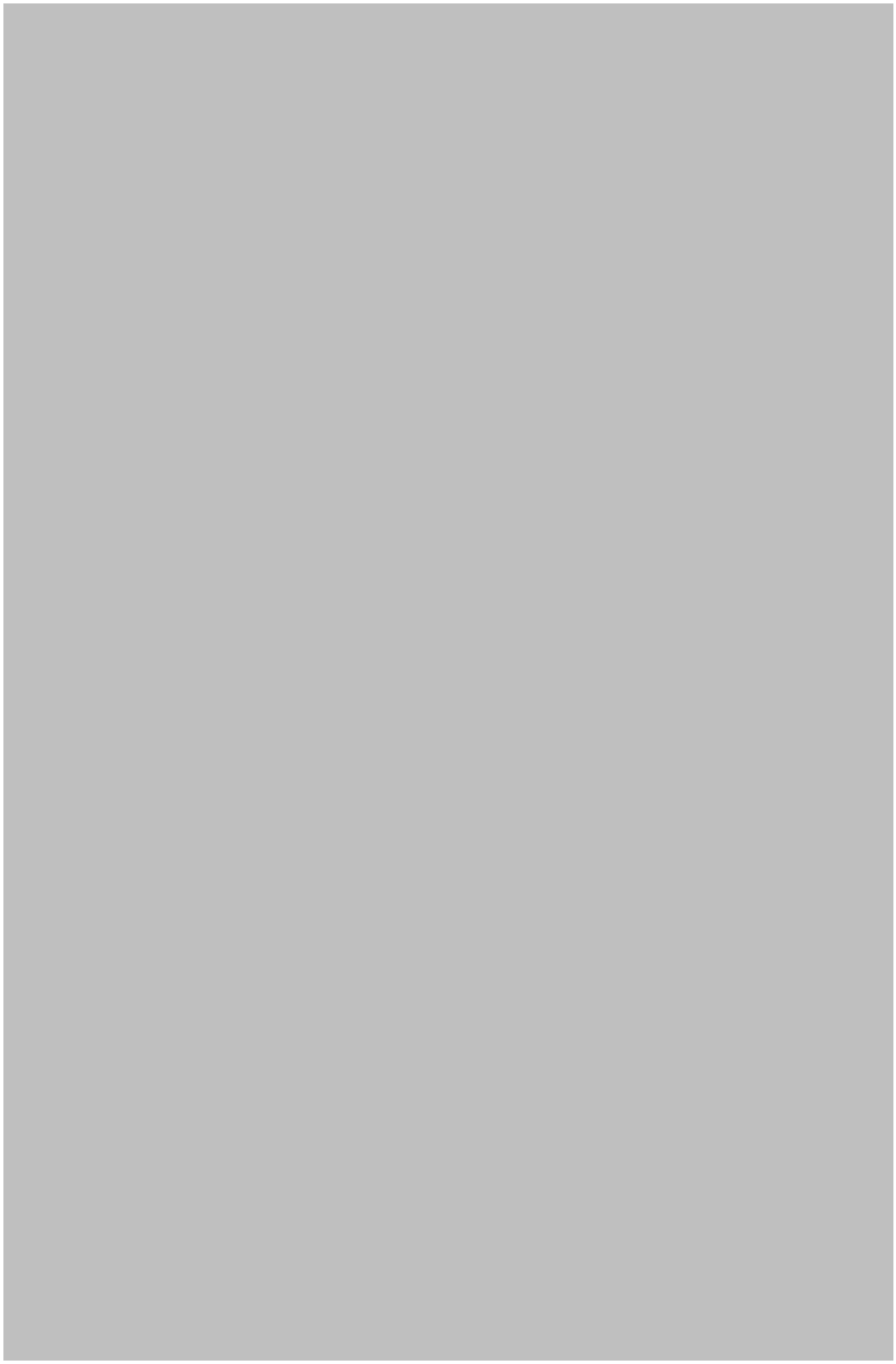
McCleery, J. P., Elliott, N. A., Sampanis, D. S., & Stefanidou, C. A. (2013). Motor development and motor resonance difficulties in autism: relevance to early intervention for language and communication skills. *Frontiers in Integrative Neuroscience*, *7*. doi: 10.3389/fnint.2013.00030

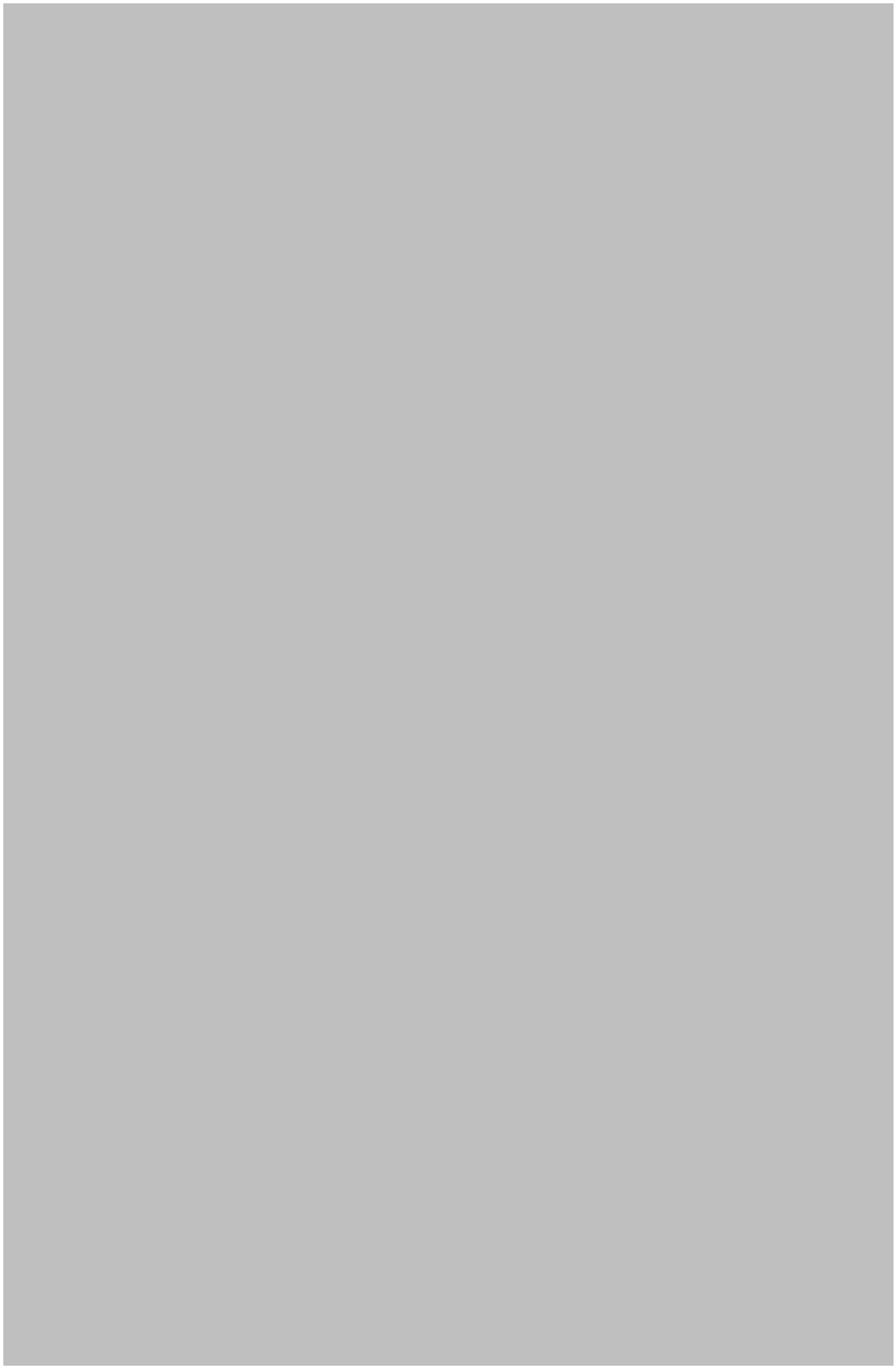
Appendix C1

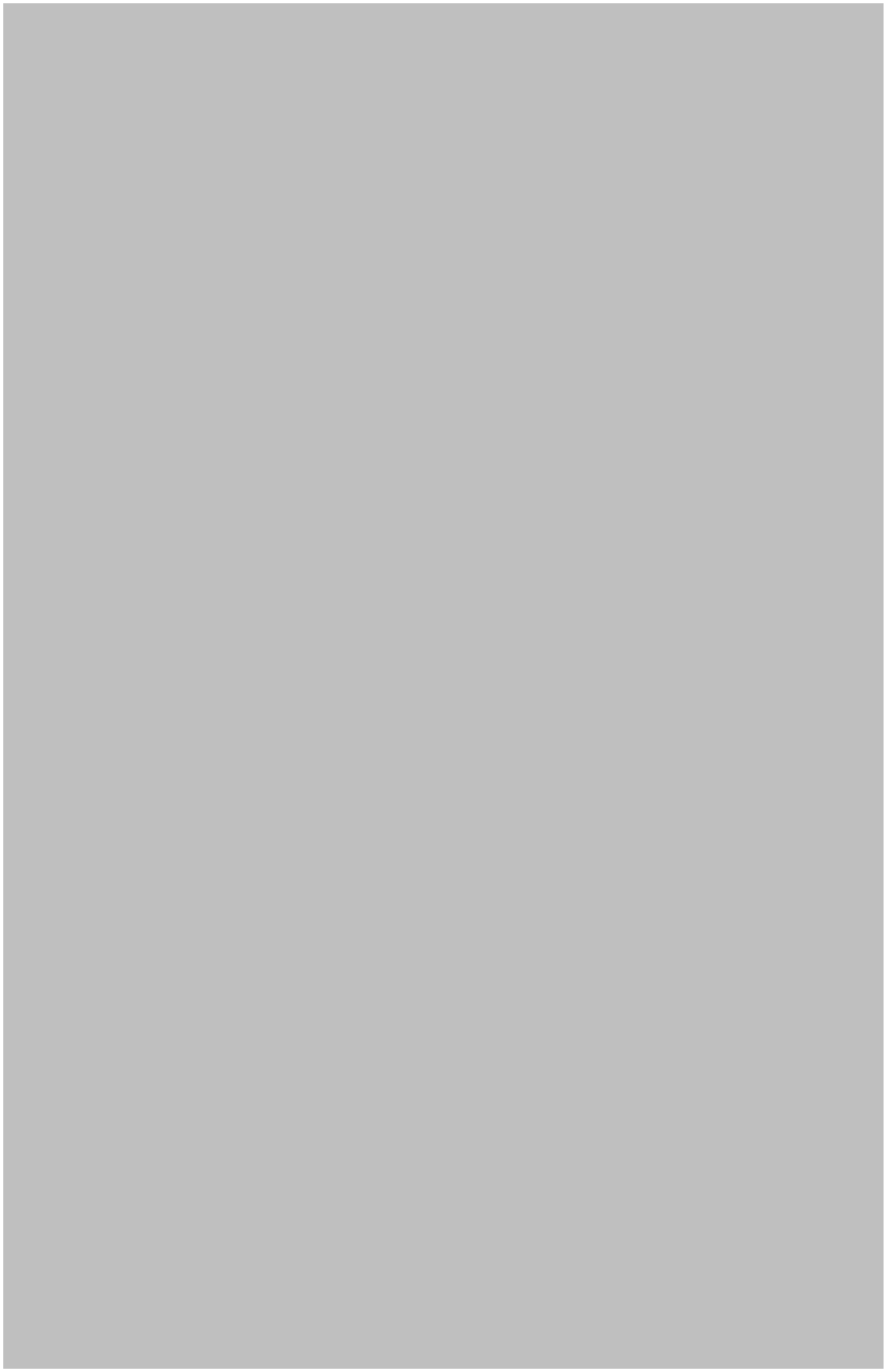


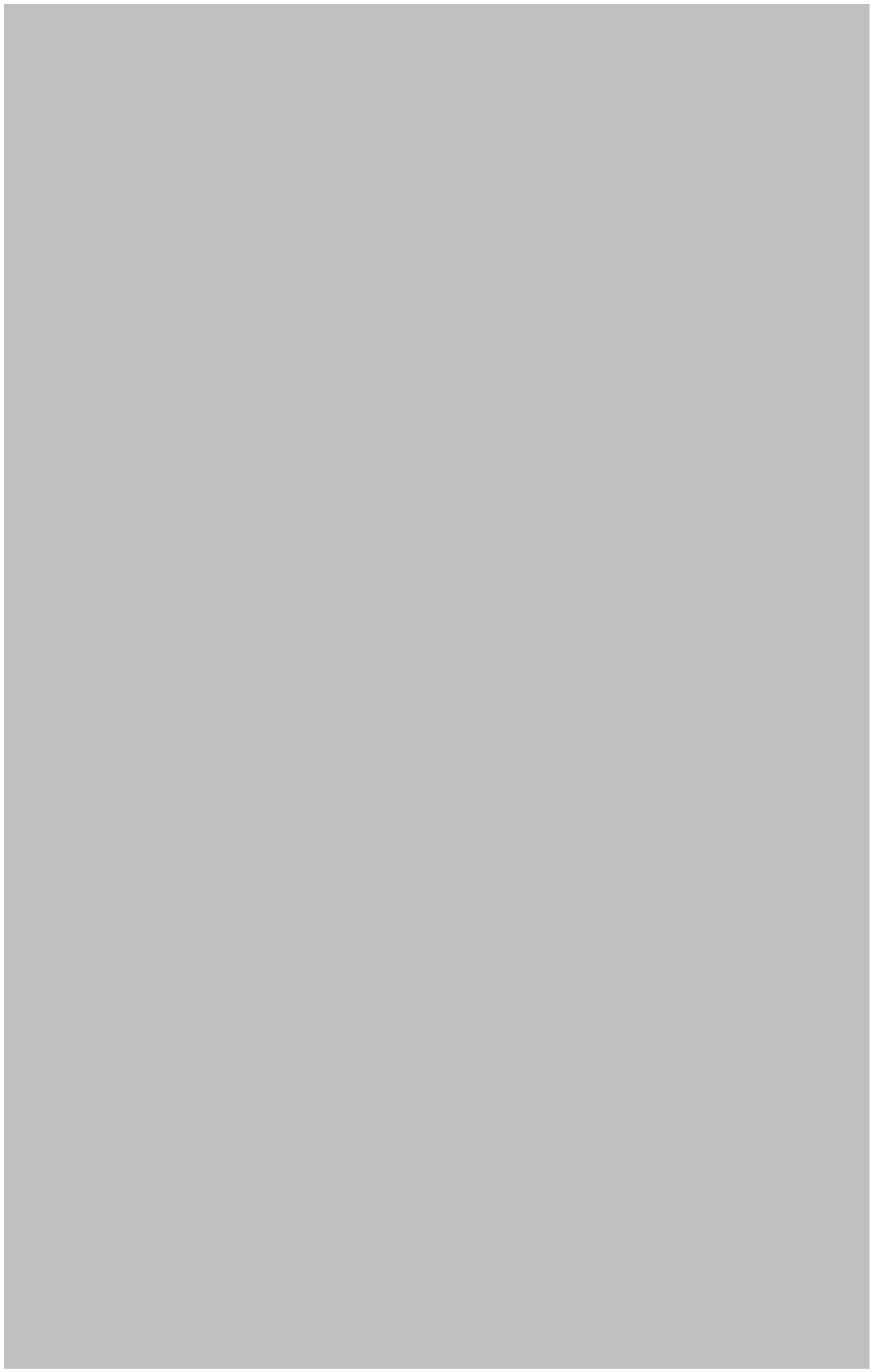


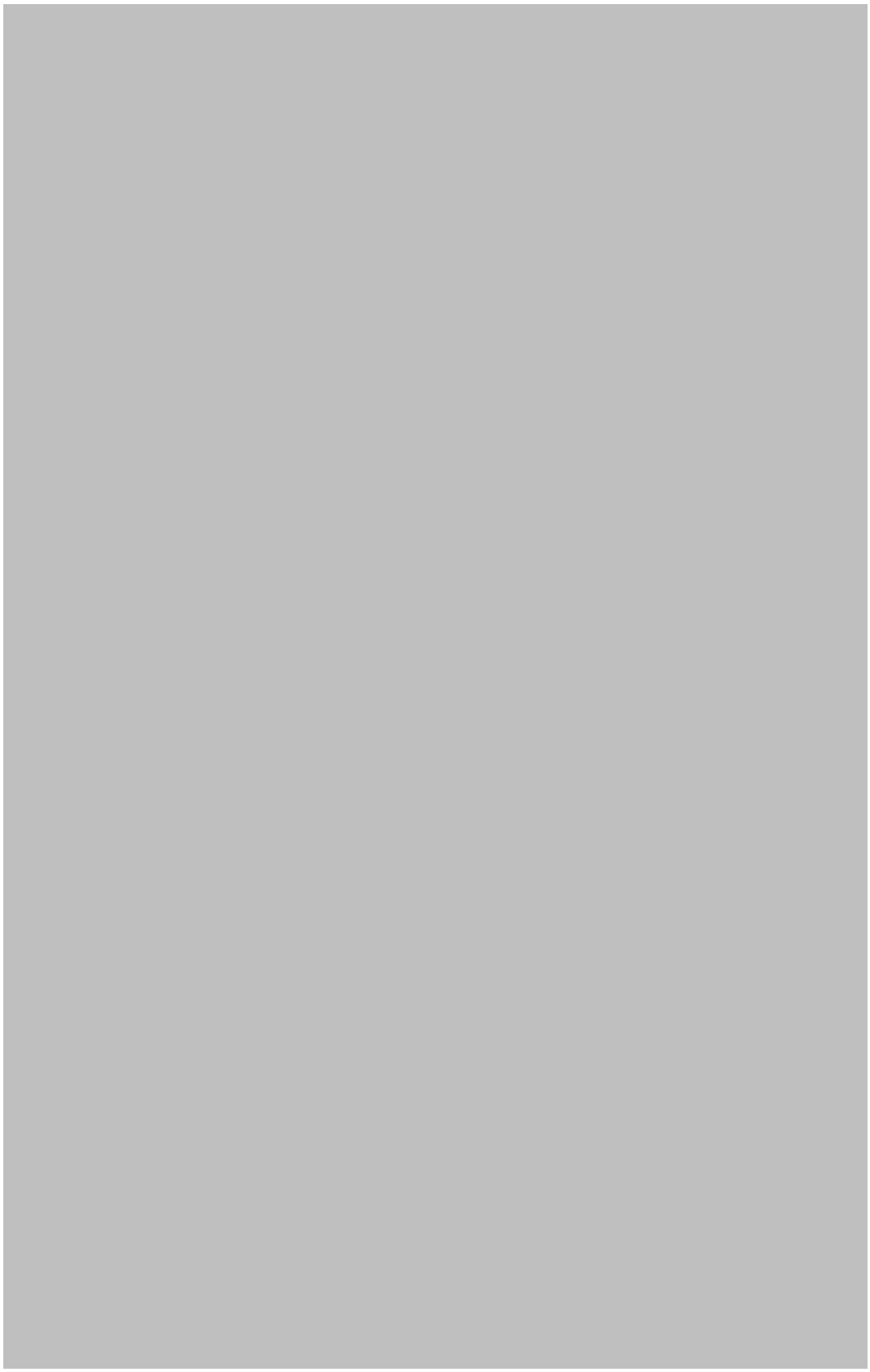


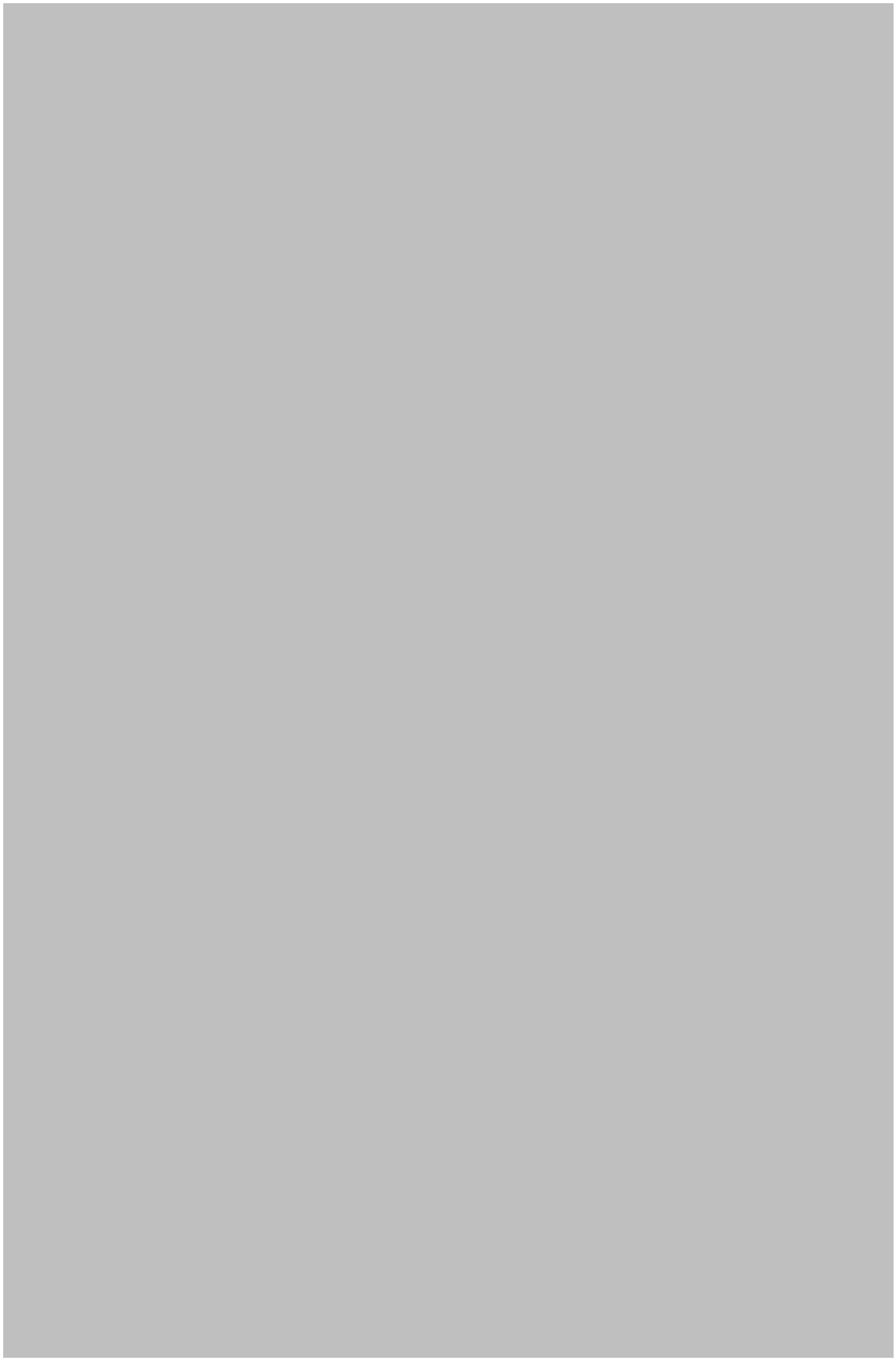


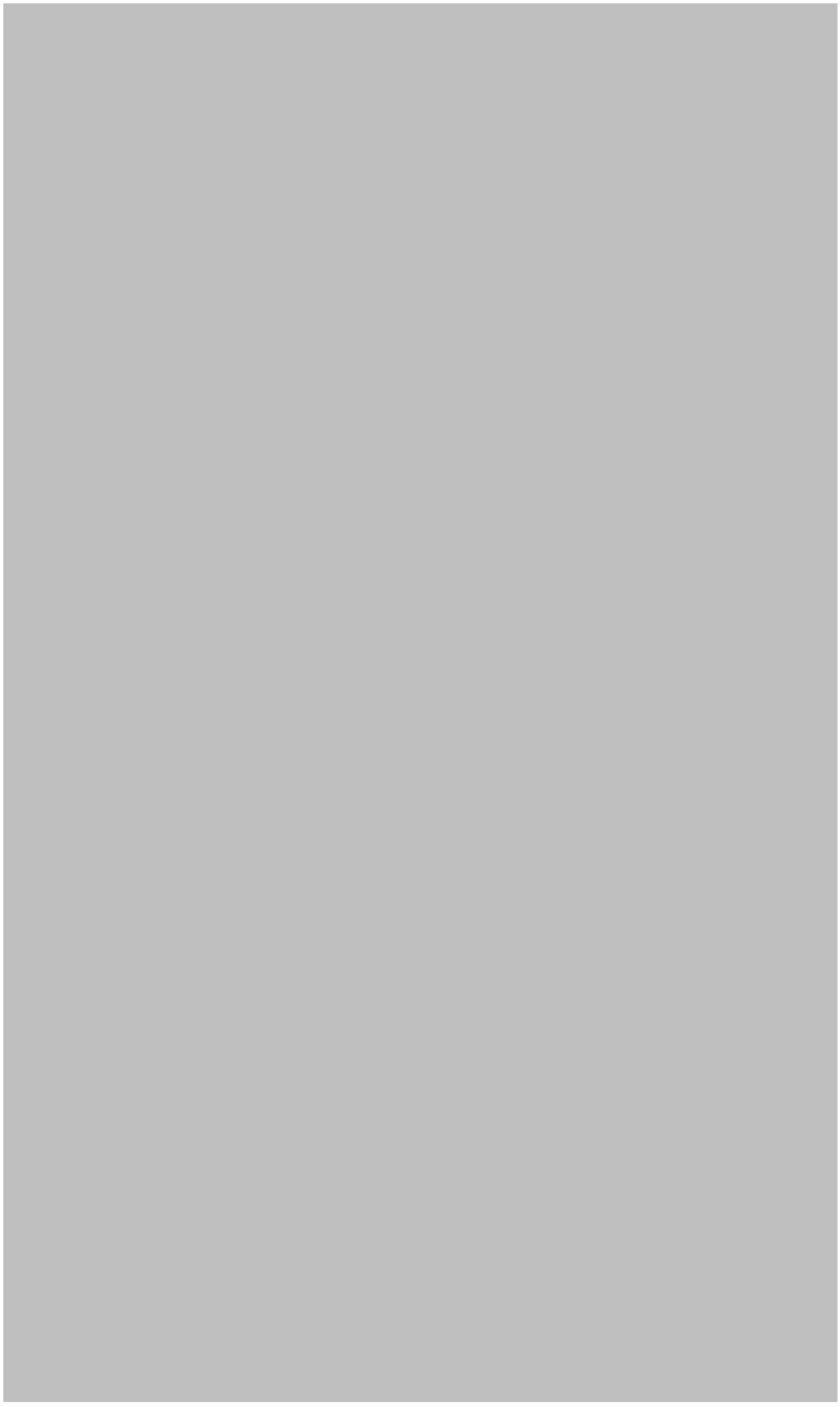


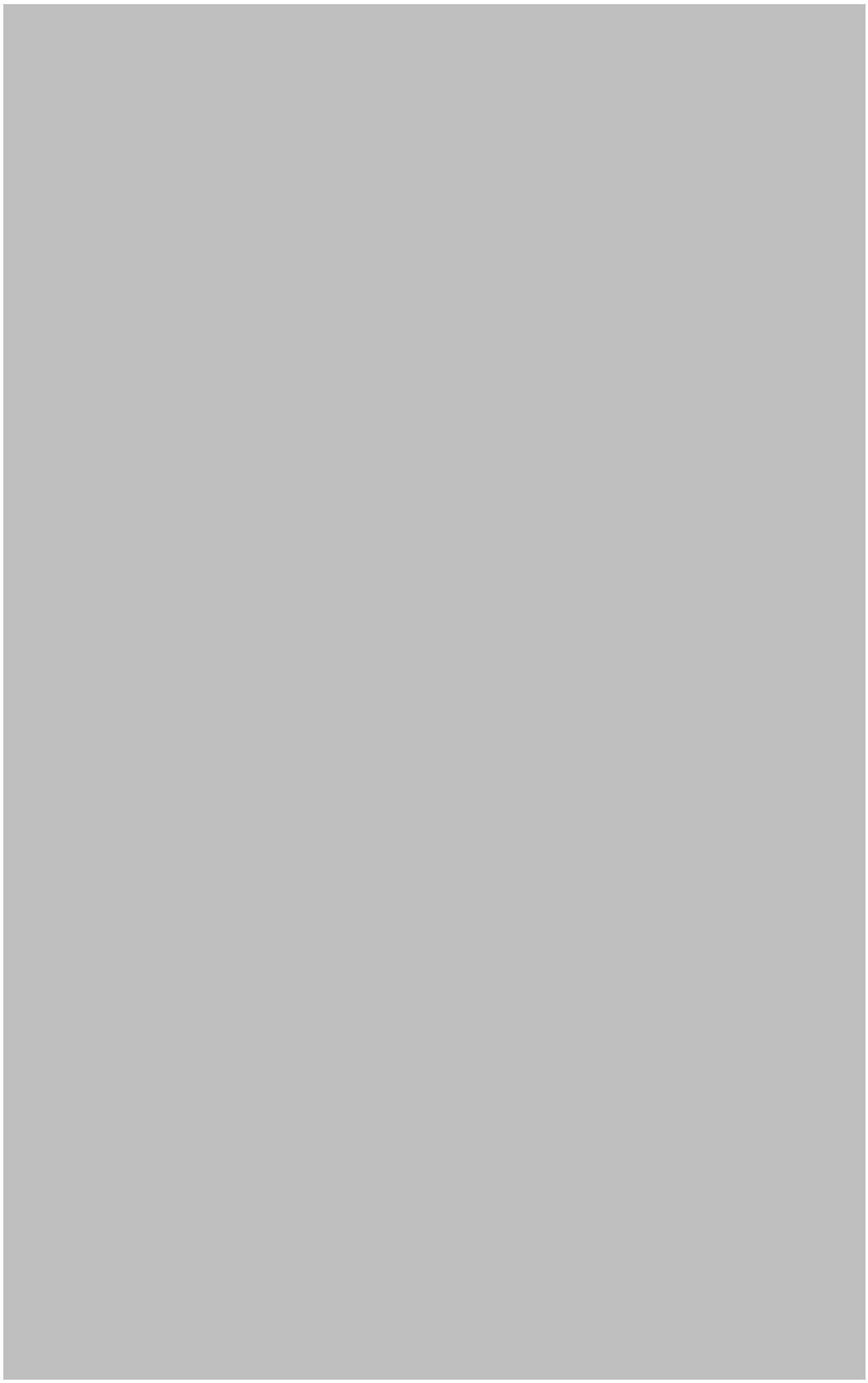


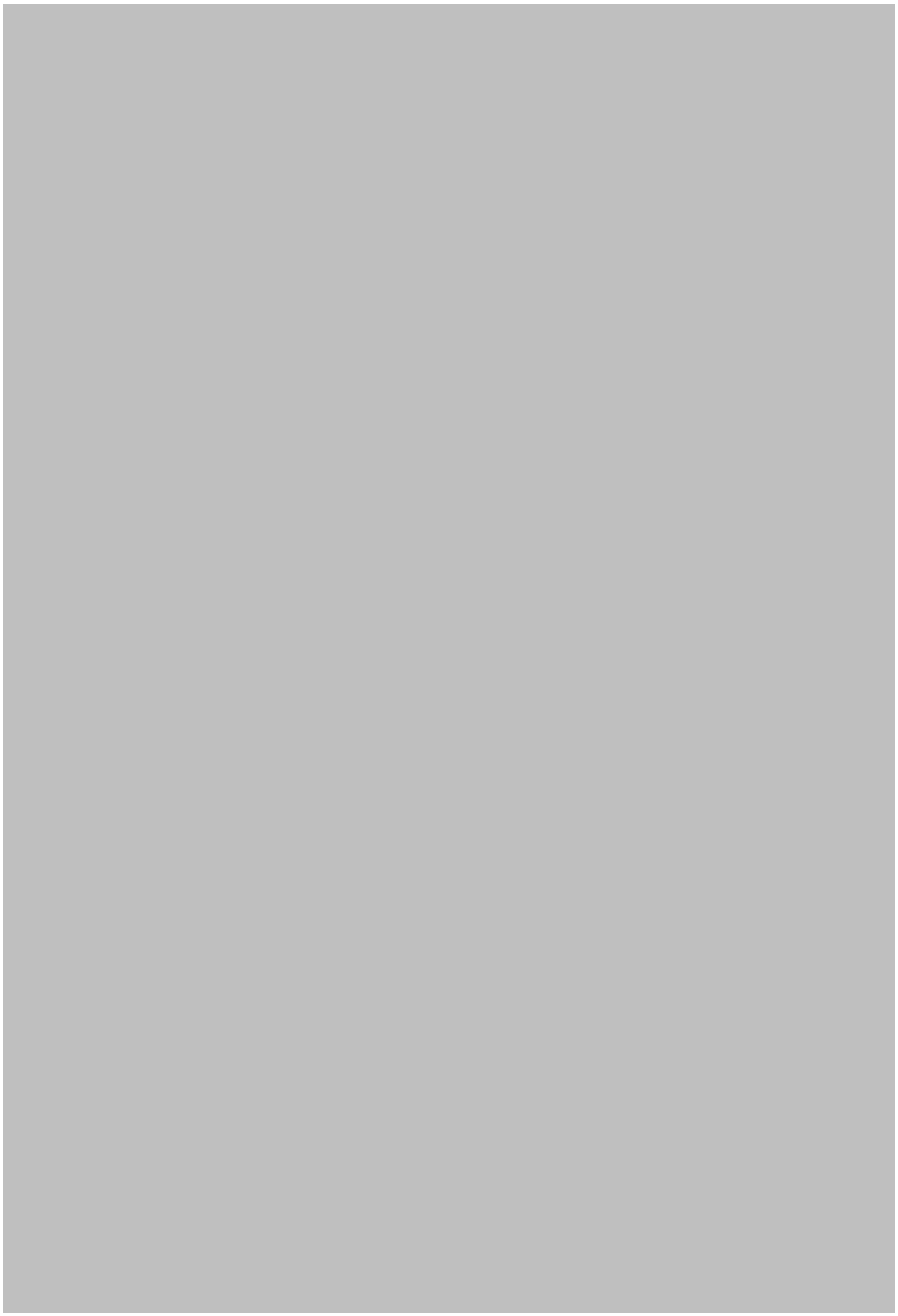


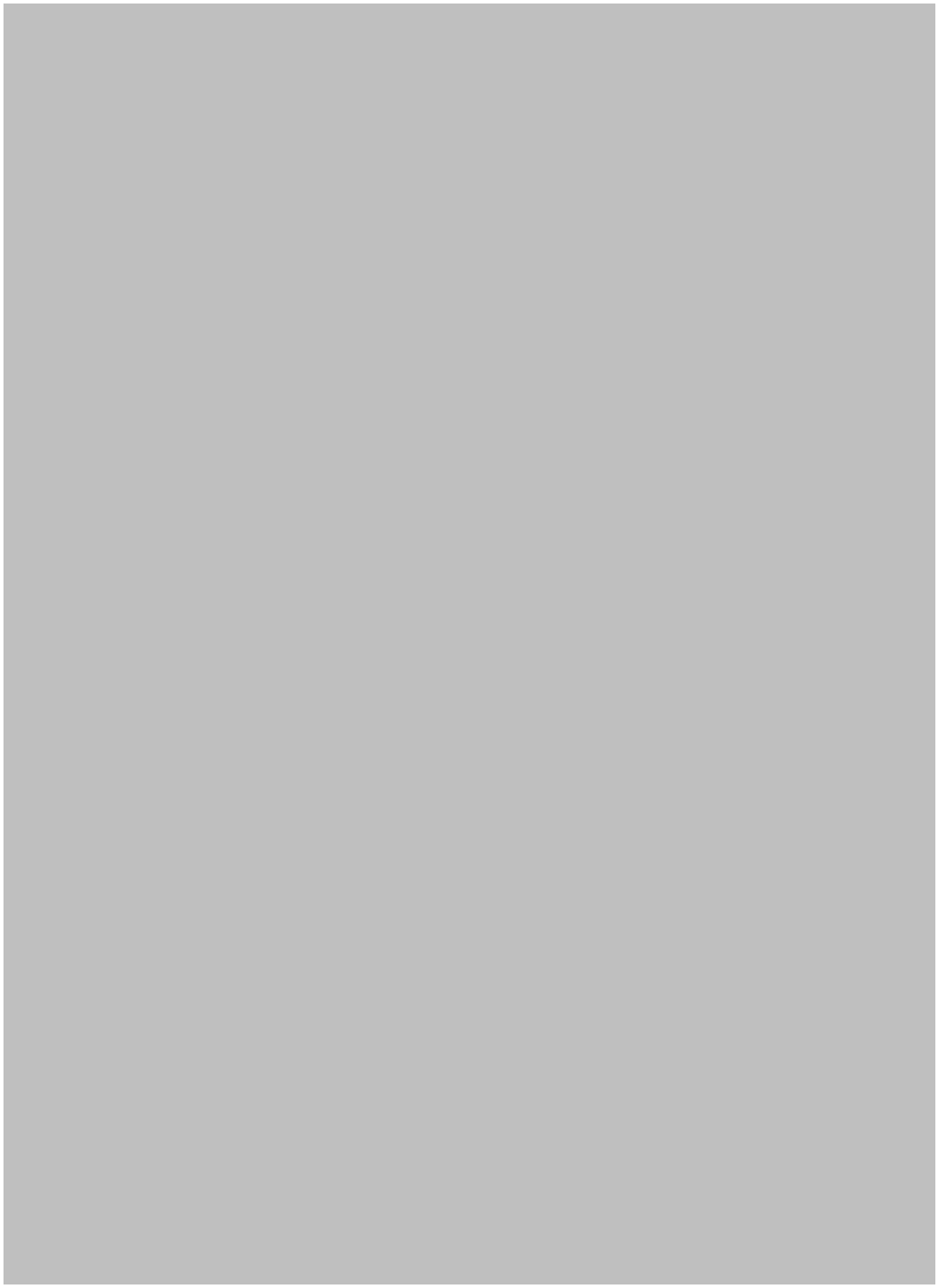


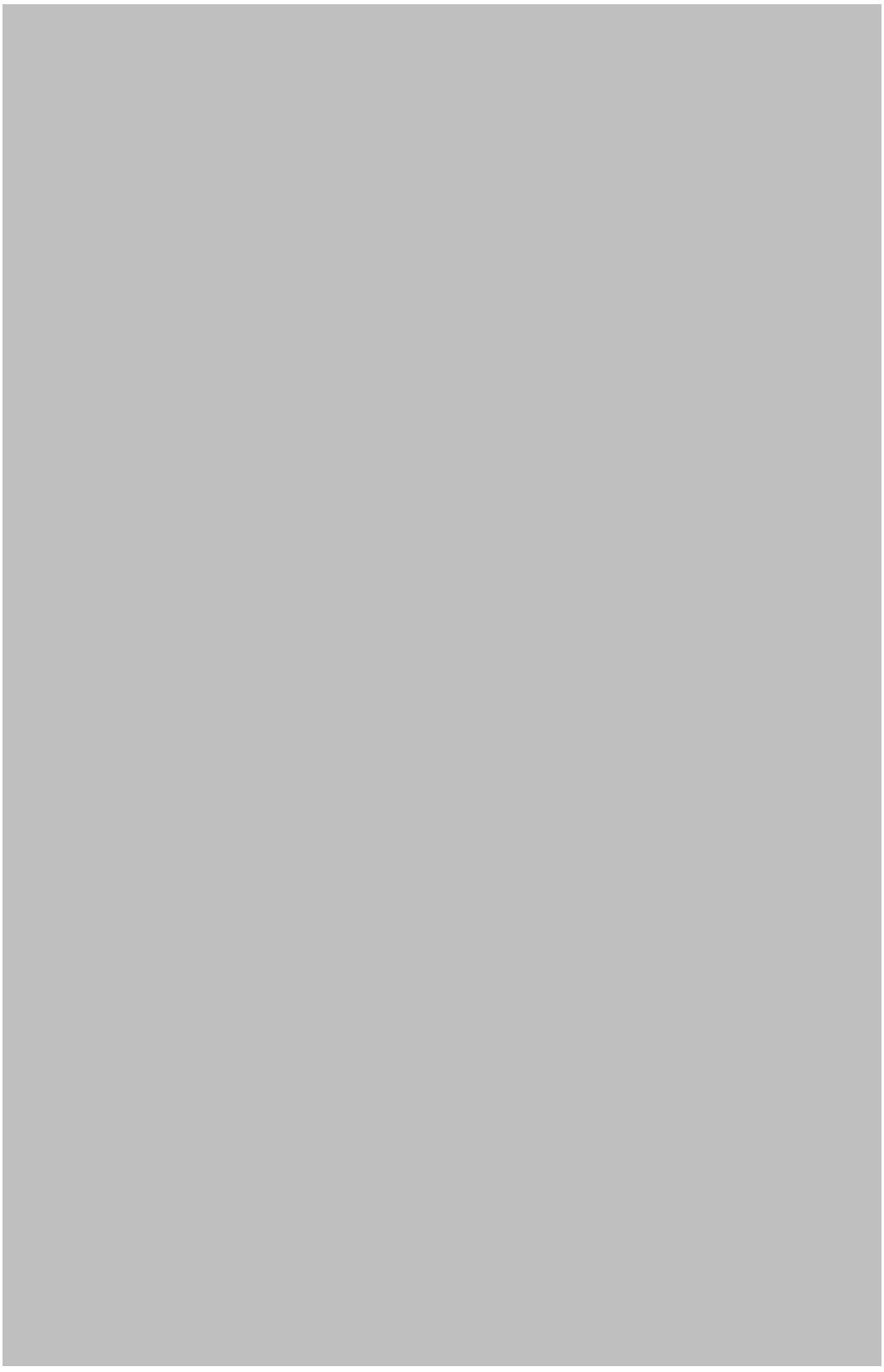


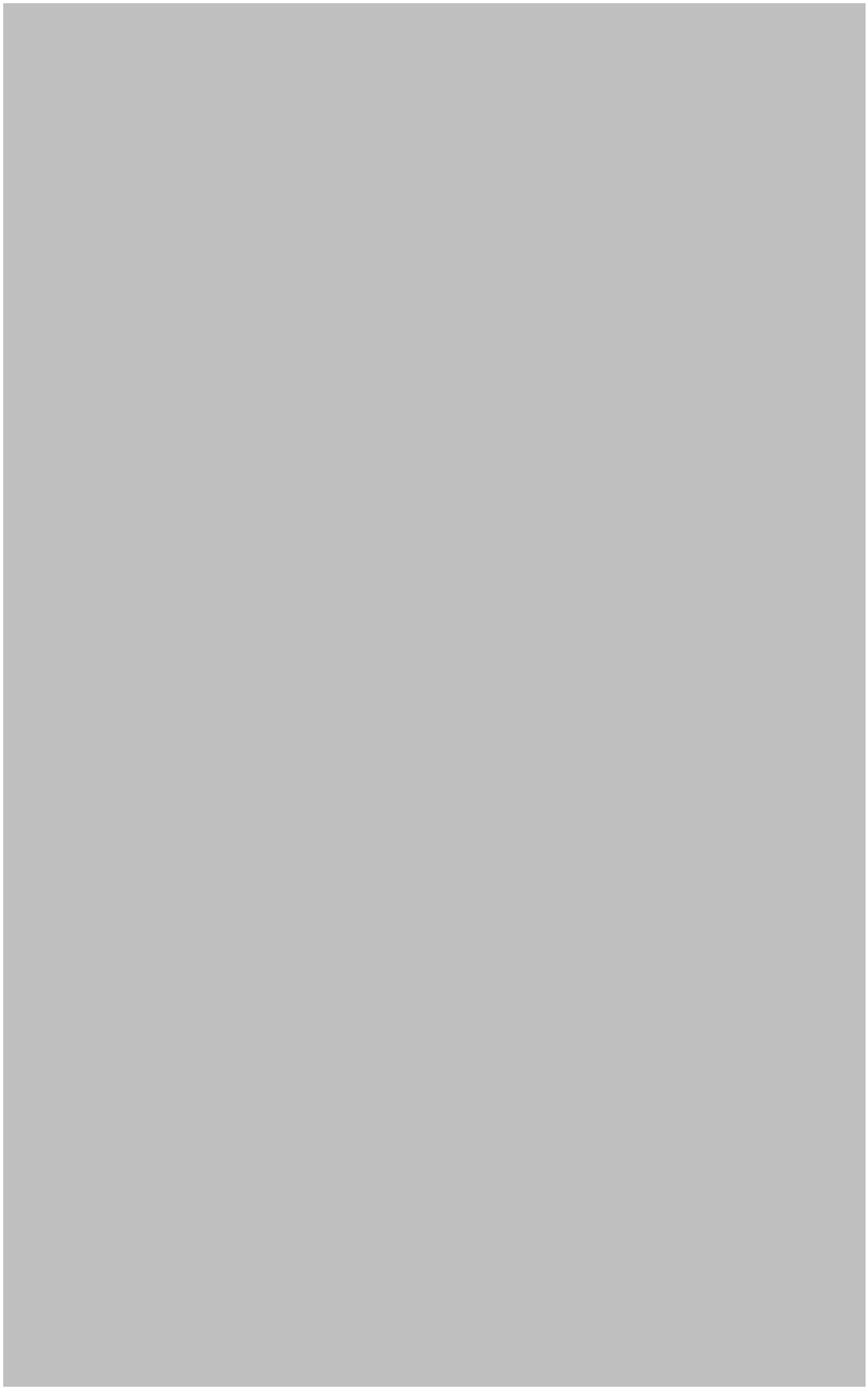


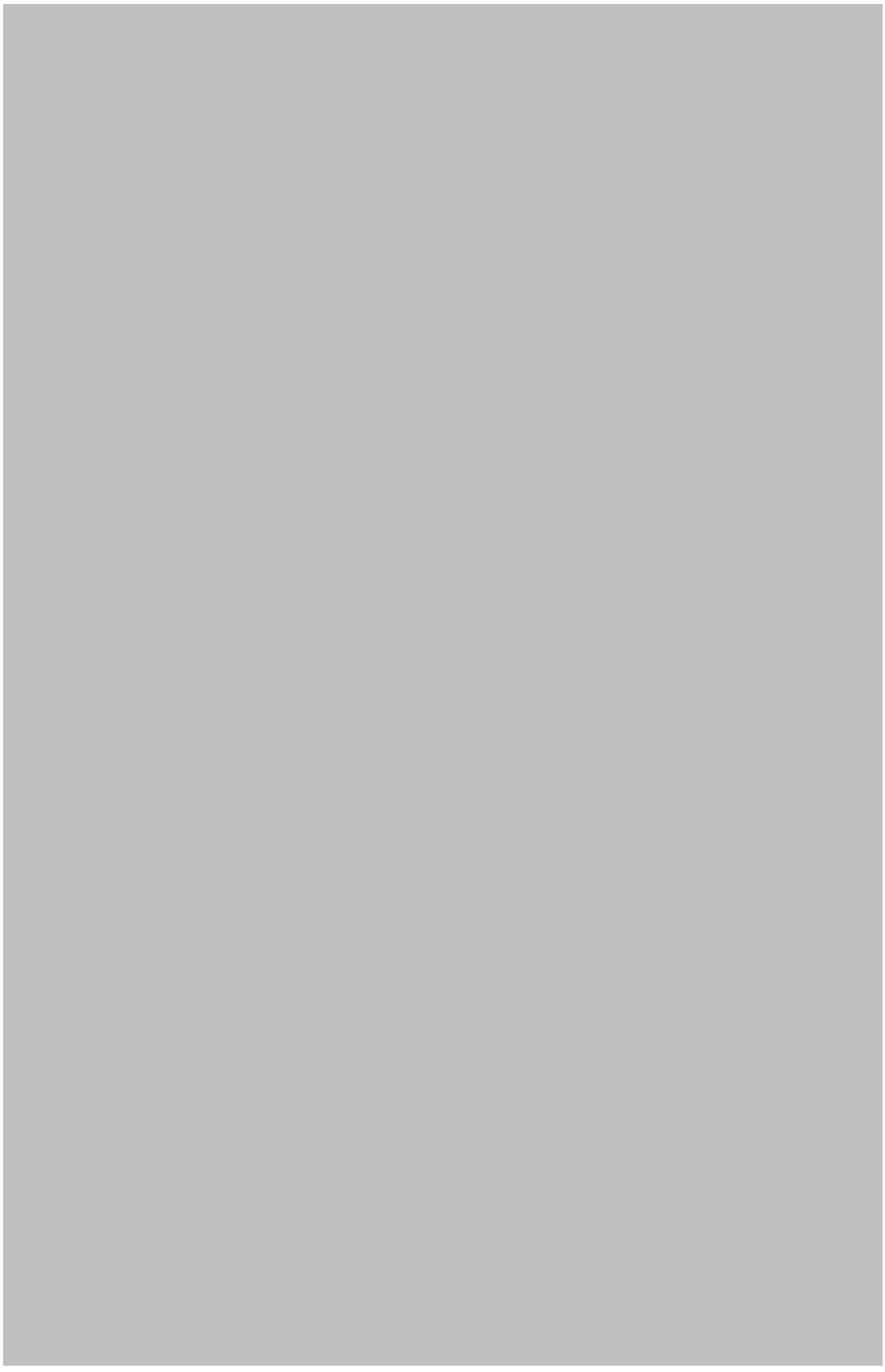


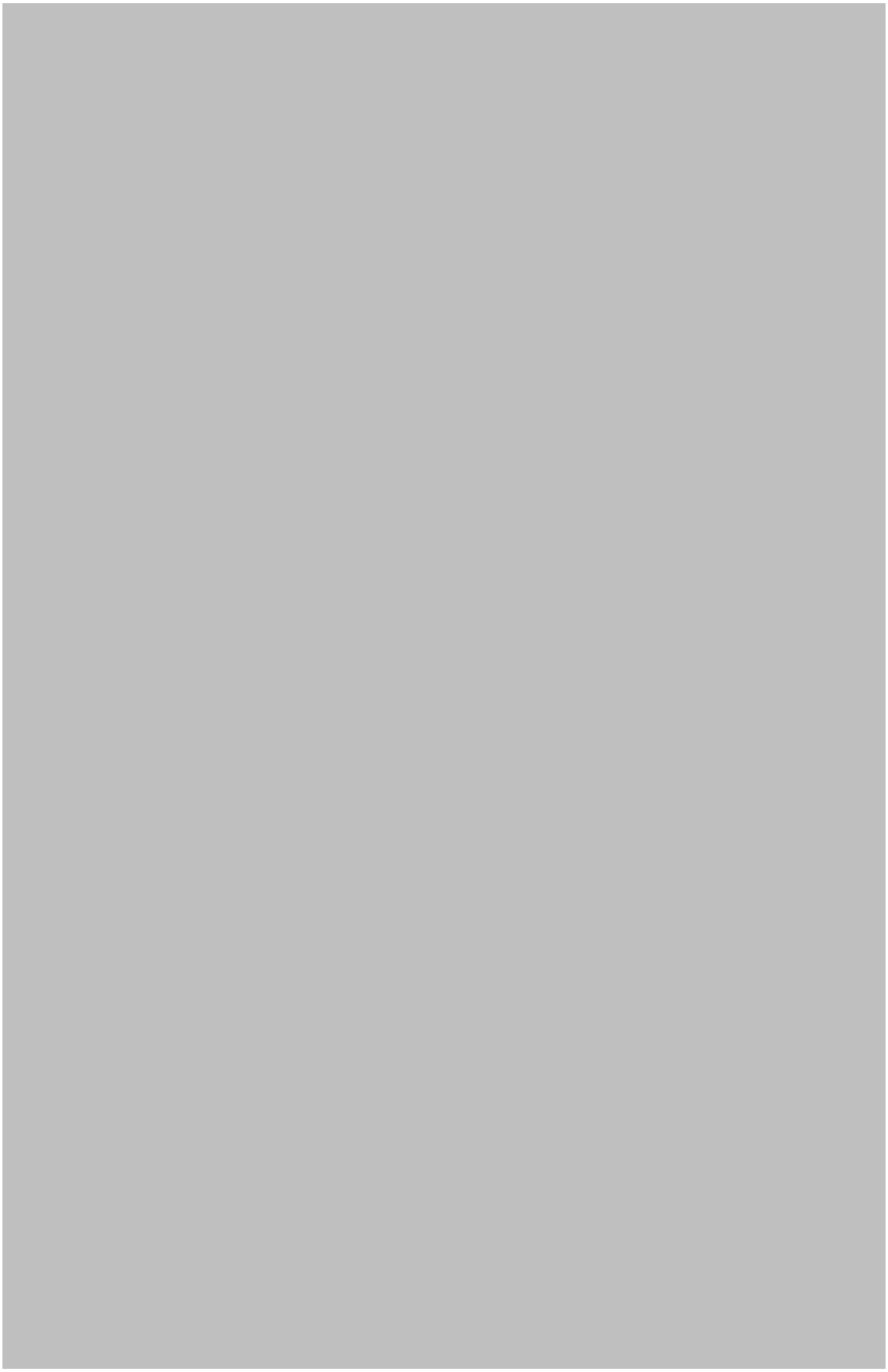












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Appendix C2