THE DEVELOPMENT OF SOCIAL PROCESSING IN YOUNG CHILDREN: INSIGHTS FROM SOMATOSENSORY ACTIVATIONS DURING OBSERVATION AND EXPERIENCE OF TOUCH IN TYPICALLY DEVELOPING CHILDREN AND SPEECH PROCESSING IN CHILDREN WITH AUTISM SPECTRUM DISORDERS

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A thesis submitted to
The University of Birmingham
for the degree of
DOCTOR OF PHILOSOPHY

School of Psychology

College of Life and Environmental Sciences

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March 2015

ABSTRACT

This thesis explores the neural mechanisms underlying the observation of touch and tactile processing in adults and typically developing children and speech versus computerized speech processing in children with autism spectrum disorders (ASD). Chapter 1 reviews the literature on mirror functioning, embodied cognition and typical and atypical development of social and speech processing in infancy and childhood. Chapter 2 investigates the neural mechanisms underlying hand and object touch observation in adults. In Chapter 3, a similar procedure is employed to investigate tactile mirroring mechanisms in children. The findings demonstrate that these mechanisms are relatively developed in 4- to 5- year old children. Chapter 4 further explores somatosensory activity during touch in adults and children. The findings reveal the modulation of somatosensory beta (15-24 Hz) activity during touch in adults, but not in children. Chapter 5 examines the neural mechanisms underlying speech versus computerized speech perception in children with ASD. These results suggest an impaired classification of speech sounds preceded by computerized speech, and atypical lateralization of speech processing in children with ASD. Together, these findings make a notable contribution to our understanding of typical development of tactile mirroring and touch processing mechanisms, and social processing dysfunctions in children with ASD.

“Somewhere beyond wrong and right, there will be a garden. I will meet you there.” Rumi

To my parents for their support, and to the memory of

my grandparents and great aunt

ACKNOWLEDGEMENTS

I would like to take this opportunity to express my gratitude to the people who have been contributed to the development of this work professionally and on the personal level.

First, I would like to thank my supervisor Dr. Joe McCleery for his guidance throughout this PhD and scientific contribution to the development of this thesis. I would also like to thank my second supervisor Dr. Andrew Bagshaw for his feedback and support provided in the final year. Special thanks go to the College of Life and Environmental Sciences, University of Birmingham for the financial support which made it possible to carry out this research.

I would like to say thank you to all my colleagues and research assistants working in the Infant and Child Lab, for their daily support throughout this PhD. Special thanks to Supriya Malik, Sissy Stefanidou, Wafa Alshami and Antonis Christou for their assistance with testings, clinical assessments and participants' recruitment and Satoshi Endo for his assistance with Matlab. I would also like to thank the Peach network and Autism West Midlands for the help with the recruitment of ASD participants and all local family support groups for parents with children with ASD who helped us to spread the word. Importantly, I am very grateful to all families who took part in this research – without you this PhD would not be possible.

I would also like to say thanks to all my friends at the University of Birmingham – it has been a pleasure to study alongside you. I am also very grateful to my family for believing in me and supporting whenever possible in my carrier. A final thank you goes to my husband Jeremy Galilee for all his patience and constant encouragement, and my mother-in-law Dorothy Galilee for her everyday support and comments on earlier versions of this thesis.

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LIST OF ABBREVIATIONS

ADOS-G – Autism Diagnostic Observation Schedule-Generic
ASD – Autism Spectrum Disorders
BAS – British Ability Scales
CA – Chronological Age
DSM-IV – Diagnostic and Statistical Manual of Mental Disorders (fourth edition)
EEG – Electroencephalography
EMG –Electromyography
ECD - Equivalent Current Dipoles
ERD – Event-Related Desynchronization
ERS – Event-Related Synchronization
ERPs –Event-Related Potentials
FFT – Fast Fourier Transformation
fMRI – functional Magnetic Resonance Imaging
fNIRS – functional Near Infrared Spectroscopy
IFG – Inferior Frontal Gyrus
IPL – Inferior Parietal Lobe
LSW – Late Slow Wave
MEG – Magnetoencephalography
MEP– Motor Evoked Potential
MMN – Mismatch Negativity
MN – Mirror Neurons
MNS – Mirror Neuron System
MSEL – Mullen Scales of Early Learning
PSD – Power Spectral Density
SI – Primary Somatosensory Cortex
SII – Secondary Somatosensory Cortex
SCQ – Social Communication Questionnaire
SEP – Somatosensory Evoked Potentials
STS – Superior Temporal Sulcus
SSG – Speech Generation Method
TD – Typically Developing
TMS – Transcranial Magnetic Stimulation
VA – Verbal Age

STATEMENT OF AUTHORSHIP

This thesis contains material that has been published[1], has been submitted[2] for publication or is currently under submission[3] to various academic journals. As a consequence, each chapter has its own abstract, introduction and discussion. Repetition of material has been avoided where possible but there may be some overlap in the background content, in particular in Chapters 2-4. The authorship on each paper indicates collaborative work. To clarify, I collected all the data (Chapters 2-4) or the majority of the data (Chapter 5), analysed the data in all of the chapters, wrote the manuscripts and I am the primary author. My supervisor Joseph McCleery is named as an author on all papers as he helped to develop these studies and provided feedback on the manuscripts. Chrysi Stefanidou is also named as an author on one of the papers[3] as she significantly contributed to ASD data collection and provided feedback on the manuscript.

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INTRODUCTION

Embodied cognition and simulation theories suggest that many human social-cognitive processes are bodily based as they are influenced by the simulation of similar processes in observer, most likely through the activation of specific neural circuitries during visual, sensorimotor and emotional experiences (Decety, 1996, Jeannerod, 2001, Svensson &Ziemke, 2004, Gallese, 2008, 2012). Mirror neurons that have been discovered in macaque monkeys discharge during both execution and observation of an action provide some additional neurophysiological basis for the embodied theories (di Pellegrino et al., 1992, Gallese et al., 1996, Rizzolatti et al., 1996, Umilta et al., 2001). It has been further suggested that mirror system, or a similar embodied system matching action observation and execution in humans (Iacoboni et al., 1999, Buccino et al., 2001, Dinstein, 2007, Decety & Grezes, 2006, Gazzola and Keysers, 2009, see also Rizzolatti & Craighero, 2004) play a role in some aspects of social cognition (Rizzolatti et al., 2002, Gallese et al., 2004, Rizzolatti & Fabbri-Destro, 2008). Specifically, it has been suggested that mirroring and simulation might play a role in understanding intentions and emotions of other people (Carr et al., 2003; Jabbi, Swart, & Keysers, 2007; Jackson, Meltzoff, & Decety, 2005; Singer et al., 2004, 2006; van der Gaag, Minderaa, & Keysers, 2007; Wicker et al., 2003). Previous research also established that some aspects of mirror functioning are diminished in individuals with autism spectrum disorder (ASD), further suggesting the role of action mirroring in the development of social-cognitive skills (Oberman et al., 2005, 2008, Theoret et al., 2005, Enticott et al., 2012, Dapretto et al., 2006, Martineau et al., 2010, Honaga et al., 2010, for a review, see Becchio & Castiello, 2012).

Following initial discoveries demonstrating the involvement of motor and premotor cortical regions in action perception, some other aspects of embodied cognition, as well as developmental trajectories of mirror functioning, have been investigated. First, several electrophysiological studies suggested the presence of mirror functioning in infants from approximately 8 months of age, and the overall establishment of matching mechanisms underlying action observation and execution in preschool and school-age children (Lepage & Theoret, 2006, van Elk et al., 2008, Nystrom et al., 2008, Nystrom et al., 2011, Marshall et al., 2011, Paulus et al., 2012, for a review see Marshall and Meltzoff, 2014). Another line of neuroimaging research demonstrated the activation of somatosensory cortices and adjacent regions during the observation of touch, suggesting the existence of a similar embodied mechanism for touch sensation in adults (Keysers et al., 2004, Ebisch et al., 2008, Ebisch et al., 2011, Schaefer et al., 2006, Gazzola et al., 2012). Although some recent magnetoencephalographic findings indicate the modulation of somatosensory activity induced by electrical stimulation by the observation of touch in 3 to 4 year old children (Remijn et al., 2014), the development of tactile mirroring mechanisms underlying the observation of touch has not yet been addressed in preschool and school-age children. Finally, neurophysiological research of touch processing mechanisms in preschool children has been limited to a few studies to date (Xiang et al., 2004, Pihko et al., 2009, Remijn et al., 2014).

The main aim of this thesis was to investigate the development of social-cognitive functions in three different domains: tactile perception and mirroring, human versus non-human processing and auditory speech processing. The neurophysiological investigation of the development of mechanisms underlying the observation of touch and tactile stimulation in young children would expand our knowledge of the nature and the role of the embodied mechanisms underlying touch perception and touch processing in social processing and

cognition. Additionally, thorough investigation of the development of the mechanisms underlying tactile stimulation in young children can expand our understanding of the nature and development of somatosensory processing in early childhood. Finally, neurophysiological investigation of social and non-social processing in auditory speech domain in children with ASD is of great importance as it could provide further insights into the nature and development of social-cognitive dysfunctions in ASD, which includes impairment and atypicalities in different domains of embodied mechanisms, such as processing social stimuli, including faces, human actions and speech in adults and children with ASD (Ceponiene et al., 2003, Kuhl et al., 2005, Lepisto et al., 2005, Lepisto et al., 2007, Lepisto et al., 2006, Kujala et al., 2013, Oberman et al., 2005, 2008, Theoret et al., 2005, Enticott et al., 2012, Webb et al., 2006, Webb et al., 2011, Castelli, et al., 2002, Freitag et al., 2008, Herrington et al., 2007). In particular, the neurophysiological mechanisms underlying speech (social) versus computerized speech (non-social) processing dysfunction in ASD might be associated with communication and social interaction difficulties which are experienced by individuals with ASD (American Psychiatric Association, 2013).

Aims and objectives

In the current thesis, an innovative event-related potential (ERP) paradigm was applied to investigate the nature and the time-course of the mechanisms underlying the observation of human and non-human touch in adults. Additionally, to address the gap in the literature on the development of the mechanisms underlying touch observation in young children, a similar ERP paradigm was applied to investigate the nature and the time-course of the observation of human and non-human touch in 4 and 5 year old children. Thirdly, EEG

was recorded during tactile stimulation in adults and 4- to 5- year old children, to further investigate somatosensory mechanisms underlying touch processing, and to explore whether the modulation of somatosensory activity found during touch observation is also present during tactile stimulation in both adults and children. Finally, ERPs were used to investigate the mechanisms underlying atypical development of neural mechanisms underlying social versus non-social processing in auditory speech domain in 4- to 6- year old children with ASD.

Study 1. The aim of the first study was to investigate the nature and the time-course of the mechanisms underlying the observation of human and non-human touch in adults. This was completed via a novel ERP assessment with visual stimuli representing human and object touch and non-touch. Tactile stimulation was also performed in the middle and at the end of the ERP assessment, in order to address the purposes of Study 3. In order to investigate somatosensory processing during touch (see Study 3), EEG data, recorded with a high-density EEG sensor net, were collected during tactile stimulation.

Study 2. The aim of the second study was to investigate the development of mechanisms underlying the observation of touch in early childhood. For this purpose, the similar ERP assessment as in Study 1, which included the presentation of videos showing human and object touch and non-touch, was conducted in typically developing children from 4- to 5- years of age. In order to investigate somatosensory processing during touch in children (see Study 3), EEG data, recorded with a high-density EEG sensor net, were also collected during tactile stimulation performed in the end of the ERP assessment.

Study 3. The third experiment builds on Studies 1-2. The main aim was to investigate whether the modulation of somatosensory activity that is seen during the observation of touch (Studies1-2) is also present during tactile stimulation in adults and children. The EEG data collected during tactile stimulation in Study 1 and Study 2 were analysed, by the implementation of the time-frequency EEG analysis. More specifically, the modulation in alpha and beta frequency bands during touch at the electrodes positioned over somatosensory cortex was examined in both adult and children groups.

Study 4. In the final study, we utilized ERPs to investigate speech (social) and non-speech (non-social) processing in children with ASD. For this purpose, an auditory ERP assessment was conducted using high-density EEG, to investigate event-related responses to auditory speech and non-speech sounds in typically developing children and children with ASD. Cognitive verbal and non-verbal skills in both groups were established before or after ERP assessment based on the results of behavioural cognitive assessments (Mullen Scales of Early Learning, Mullen, 1995; British Ability Scales, Elliott, Smith & McCulloch, 1997).

Thesis structure

Chapter 1 represents a comprehensive review of the literature on neurophysiological research studies of action observation/execution and touch perception in adults, based on mirror neuron theory and embodied cognition and simulation approaches. The second section of the literature review discusses literature on neuroanatomical and neurofunctional social brain development, specifically the developmental mechanisms underlying social information processing, tactile and speech perception. Finally, the third part of *Chapter 1* presents literature on atypical development and impairments of mirror functioning, action and speech processing in individuals with ASD.

Chapter 2 presents *Study 1* investigating the time-course of the mechanisms underlying human and object touch observation in adults.

Chapter 3 presents *Study 2* in which we employ a similar ERP procedure as in Study 1 allowing investigation of the mechanisms underlying human and object touch observation in typically developing children.

Chapter 4 presents *Study 3* in which we employ EEG time-frequency methods to look at the modulation of somatosensory activity during tactile stimulation in adults and children.

Chapter 5 presents *Study 4* investigating neural mechanisms underlying speech and non-speech processing dysfunctions in children with ASD.

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

Ethical approval

All experimental studies (Chapters 2-5) were approved by the Ethical Review Committee of the University of Birmingham. Some families with children with ASD who participated in the research in Chapter 5 were recruited from Birmingham and the surrounding districts of the West Midlands, through the distribution of research subject recruitment flyers which were approved by the University of Birmingham Internal Review Board (IRB). All adult participants and parents of all children who participated in this research were asked to sign an approved consent form to approve their or their child's participation in the study *(see Appendices A).*

CHAPTER 1:

GENERAL INTRODUCTION

1.0 Introduction

The embodied self represents a concept describing an enactive approach to cognition, emphasizing the bodily experiences influence the social-cognitive functioning. The experimental support for embodied cognition and embodied simulation theories comes from behavioural and neurophysiological research suggesting the presence of neurophysiological simulation mechanism which activates similar neural circuitry during both observation of experiences of others and our own experiences (Decety, 1996, 2002, Gallese, 2012). Additionally, direct evidence from single cell recording of a monkey's brain as well as the indirect combined evidence from many neuroimaging, electrophysiological, and transcranial magnetic stimulation studies suggest the existence of a matching set of neurons, the mirror neurons in monkeys and a similar embodied matching system in humans, which respond selectively to both execution and observation of an action (Gallese et al., 1996, Iacoboni et al., 1999, Buccino et al., 2001, Dinstein, 2007, Decety & Grezes, 2006, Hari & Kujala, 2009, Gazzola and Keysers, 2009, see also Rizzolatti & Craighero, 2004). It has been suggested that the embodiment is limited to the perception of other people's actions, but might also play a role in some aspects of social cognition, including understanding other people's emotions and sensations (for a review, see Keysers & Fadiga, 2008, Keysers & Gazzola, 2009). More specifically, recent neuroimaging and electrophysiological research has demonstrated the activation of the somatosensory cortices during both observation and the experience of touch (Keysers et al., 2004, Ebisch et al., 2008, Ebisch et al., 2011, Bufalari et al., 2007, Pihko et al., 2010). This set of discoveries initiated research into the functional properties of the mirroring mechanism in somatosensation and opened up new possibilities to explore the development of putative mirroring mechanisms for action and touch observation in typical and atypical development from infancy to adulthood. In particular, some aspects of action

mirroring have been shown to be diminished in children and adults with an autism spectrum disorder (ASD) (Oberman et al., 2005, Oberman et al., 2008, Dapretto et al., 2006, Bastiaansen et al., 2011, Martineau et al., 2010). Notably, ASD has been characterized by severe behavioural dysfunctions in social and communication skills (American Psychiatric Association, 2013). Thus children with ASD represent an interesting sample for studying speech and language development as well the role of embodied mechanisms, including mirror functioning in social cognition. The present review outlines mirror neuron and embodied cognition theories and discusses previous findings of behavioural and neurophysiological studies supporting these theories, as well as the development of social processing in the domains of tactile and speech perception, in young infants and children, in order to explore further social cognition in typical and atypical development. Finally, this review discusses the existing literature investigating the neurophysiological mechanisms of speech (social) and non-speech (non-social) processing in ASD, in order to underpin the nature of social processing difficulties, including social attention, human and biological action processing in ASD.

1.1 Mirror system and its possible role in social cognition

1.1.1. First discovery

The mirror neurons (MN) were initially discovered in the area F5 in a macaque monkey brain by a group of neuroscientists in the University of Parma. These neurons were discovered as a by-product in the study that looked at the neurons in premotor cortex which

discharged during the execution of goal-directed actions (di Pellegrino et al., 1992). Additionally, the authors found that 10% of neurons in the premotor cortex had 'mirror like' properties and discharged during both execution and observation of a goal directed action. Following this initial discovery, a series of studies investigated different properties of MN in the ventral premotor cortex (Gallese et al., 1996, Rizzolatti et al., 1996, Umilta, 2001) and inferior parietal lobe (Gallese et al., 2002, Fogassi et al., 2005). In particular, it has been shown that MN respond to specific goal-directed motor acts, such as grasping, manipulating and placing (Gallese et al., 1996). In other words, in most neurons (92% of neurons with mirror properties) there was a clear relationship between the visual action they respond to and the motor act they code. Interestingly, it is in this work that the notion of the MN system first appeared, with the authors' suggestion that "the mirror neurons form a system for matching action observation and execution" (Gallese et al., 1996). Moreover, taking into consideration the homology between monkey's F5 area and Broca's area, it was suggested that this system plays an important role in the understanding of actions and phonetic gestures (Gallese et al., 2004, for a review see Keysers & Fadiga, 2008).

In the current thesis, we acknowledge the fact that a single cell recording of mirror neurons in monkeys and neuroimaging and neurophysiological studies of action observation and execution in humans might not examine the same processing. However, it is likely that action observation-execution system in humans is related to mirror neurons, and therefore the underlying processes in humans are referred to as action mirroring, mirroring mechanisms or mirror system in the current thesis.

1.1.2. Direct evidence in humans

Because of the invasive nature of single cell recording, there is no direct evidence for MN in the motor cortex in healthy humans. The only direct evidence for MN in humans comes from the single-cell recording in epileptic patients undergoing surgery (Mukamel et al., 2010). In this study, extracellular activity in the medial frontal and temporal cortices was recorded while patients observed or executed a grasping action and emotional facial expressions. A significant proportion of cells in the motor area (14 %) and hippocampus (11%) represented a matching set of neurons that responded to both execution and observation of the same action. From the results of this study, taken together with single-cell recordings in monkeys, it was concluded that these neurons in ventral premotor and inferior parietal area are included in the matching system, the mirror neuron system (MNS) that makes a self –other comparison and distinction.

1.1.3. TMS evidence

The first evidence for mirroring mechanisms in humans comes from transcranial magnetic stimulation (TMS) studies showing a modulation of a corticospinal excitability with action observation (Fadiga et al., 1995). In this study, motor evoked potentials (MEPs) were recorded from hand muscles while the motor cortex was stimulated in four different conditions: 1) when participants observed an experimenter grasping 3D-objects; 2) looked at the same 3D-objects; 3) observed an experimenter tracing geometrical figures in the air with his arm; 4) detected the dimming of a light. The authors found that MEPs were significantly increased in the conditions 1 and 3 when participants observed a hand movement. Moreover,

the MEP patterns reflected the pattern of muscle activity during execution of the observed movements.

Additionally, several TMS studies have shown that the human mirror system, unlike that of monkeys, responds also to the movement with no evident goal (Fadiga et al., 1995, Gangitano et al., 2001, Strafella & Paus, 2000). In particular, in Gangitano and colleagues' study, a video of a reaching-grasping action was shown and TMS was delivered during the action observation (Gangitano et al., 2001). The results showed that the amplitude of the MEPs was modulated by the amount of the observed finger aperture. Moreover, Strafella and Paus showed that changes in MEPs during action observation were specific to the muscle involved in the observed action (Strafella & Paus, 2000). Thus action execution-observation matching system found in TMS studies in humans might resemble the one, previously described in monkeys (Gallese et al., 1996, Rizzolatti et al., 2002).

A recent study has also investigated whether the motor cortex was activated when the participants viewed hand movements with emotional component and without an interactive context (Enticott et al., 2011). It was shown that there was an increase of the corticospinal excitability during the observation of the movement with emotional context which further suggested the role of the emotional component in MN response (Enticott et al., 2011). Additionally, another TMS study by the same group suggests that the recognition of static facial expressions correlated with enhanced motor response (Enticott et al., 2008). These findings were taken as evidence that the MN might facilitate emotion recognition in humans. Recently, Naish and colleagues reviewed the findings of 85 TMS and peripheral nerve stimulation (PNS) studies of the human mirror system response and suggested a model in order to expain how action observation modulates corticospinal excitability (Naish et al., 2014). Specifically, the authors proposed that the observation of an action elicit an early non-

specific response (before 90 ms), followed by a later modulation of corticospinal activity (after 200 ms) which is specific to the muscles involved in the observed action (Naish et al., 2014).

1.1.4. fMRI and EEG evidence

A great deal of neuroimaging research has uncovered evidence for overlap in the activity in various brain regions during action execution and observation (Iacoboni et al., 1999, Buccino et al., 2001, Dinstein, 2007, Frith & Frith, 2010, Hari & Kujala, 2009, Gazzola and Keysers, 2009, see also Rizzolatti & Craighero, 2004). These areas have included inferior frontal, inferior parietal, and ventral premotor areas, activated during the observation of goal-directed motor actions or by listening to action-related sounds (see Rizzolatti & Sinigaglia, 2010, for a review). Neuroimaging studies have also demonstrated the existence of a system matching observation and execution, by revealing the activation in the inferior parietal and premotor cortex (Buccino et al., 2001, Gazzola and Keysers, 2009). In particular, Buccino and colleagues examined the activation of the premotor cortex during the observation of both object and non-object related foot, mouth and hand actions (Buccino et al., 2001).The results showed the activation of the premotor and parietal cortices in a somatotopic manner. A more recent study utilized an fMRI adaptation paradigm to access an overlap of the cortical responses to the observed and executed actions (Dinstein et al., 2007). A sub-set of areas including premotor area and intraparietal sulcus exhibited the same repetition suppression effect (attenuation of the activity for a repeated action) during both execution and observation of the same action. Altogether, the existing fMRI evidence suggests the existence of the visuomotor matching system that responds selectively to the observation and execution of an

action. The same group suggested that the cross-modal adaptation paradigm, that is the paradigm showing an attenuation of neural activity during the execution immediately following the observation, provides stronger evidence for the existence and functions of the MN in the human brain (Dinstein et al., 2008). The logic of this approach is that as stimuli that evoke activity in a specific neuronal population are repeated, the magnitude of the response decreases or adapts (Grill-Spector et al., 2006, Dinstein et al., 2007, Dinstein et al., 2008).

fMRI adaptation effects have been reported when the observed actions are repeated (Hamilton and Grafton, 2006, Hamilton and Grafton, 2008, Dinstein et al., 2007) and when the executed actions are repeated (Dinstein et al., 2007). A recent study used an fMRI adaptation paradigm to specifically look at the repetition suppression effects in the inferior frontal gyrus (IFG), the region that is homologous to monkey's F5 area (Kilner et al., 2009). This study demonstrated consistent repetition suppression in the IFG area in each participant which is consistent with the existence of mirror neurons in human IFG (Kilner et al., 2009).

Previous fMRI studies have reported activations with similar properties in the parietal cortex (Iacoboni et al., 1999, Buccino et al., 2001, Buccino et al., 2004, Gazzola & Keysers, 2009), as well as the superior temporal sulcus (Jellema & Perret, 2003). Taken together, these data suggest that action observation-execution matching system may in fact be part of a broader network responsible for biological motion and perception (Fagg & Arbib, 1998, Oztop & Arbib, 2002). Interestingly, a recent review presented a meta-analysis of 125 fMRI studies investigating brain regions with the mirror properties (Molenberghs et al., 2012). The results revealed the clusters of activations located in 9 Brodmann areas which included "core areas" with the mirror properties such as IFG, inferior parietal lobe (IPL) and ventral premotor cortex, which is consistent the results of single-cell recordings in monkeys (Fogassi

et al., 2005, Gallese et al., 1996, Rizzolatti et al., 1996). Additionally, the part of limbic system, cerebellum and visual cortex were recruited which allows to suggest the presence of extended non-motor related mirroring mechanisms in humans, compared to MNS in monkeys (Molenberghs et al., 2012).

Neuroimaging research has contributed significantly to the understanding of mirror neuron functioning, however EEG is a significantly less expensive and easier tool to use with children and infants (Nelson & McCleery, 2008).The researchers have identified a putative index of mirror functioning in the EEG and MEG sensory-motor alpha (mu) rhythm. Examining the functional properties of the EEG/MEG mu rhythm has expanded our knowledge of important features of human mirroring mechanisms. The adult EEG mu rhythm occurs in the range 8-13 Hz and is usually recorded from the central sites (C3, C4, Cz). It has been known since 1954 that the mu rhythm is reduced in amplitude during movement (Gastaut et al., 1954). The reduction of the mu rhythm over central sites is believed to be caused by the desynchronisation of the brain activity associated with movement related information (Pfurtscheller & Lopes da Silva, 1997). Unlike the occipital alpha, this rhythm is minimally affected by dark/light eyes change and eye closing (Kuhlman, 1978). Following its initial discovery, several other studies have shown the attenuation of the sensory-motor alpha (mu rhythm) during both the execution and observation of an action or intransitive movement (Babiloni et al., 2002, Bernier et al., 2007, Calmels et al., 2006, Cochin et al., 1999, Fan et al., 2010, Muthukumaraswamy & Johnson, 2004, Muthukumaraswamy et al., 2004, Perry & Bentin, 2009; Pineda et al., 2000; Streltsova et al., 2010). Additionally, previous EEG studies demonstrated the modulation of the sensory-motor alpha rhythm according to the degree of social relevance of the stimuli (Kilner et al., 2006, Oberman et al., 2007) and in proportion to the motor expertise of the observer during the observation of bodily movements (Orgs et al.,

2008, Babiloni et al., 2009), This recent work is also based on earlier magnetoencephalography (MEG) research which demonstrated the activation of motor cortex during the observation of another person's action (Hari et al., 1998, Hari, 2006). This finding has led to further investigation of the mu EEG rhythm and other related oscillations, such as the higher frequency beta rhythm over sensory-motor and somatosensory areas. Specifically, it has been shown that modulation in low and high beta (12-30 Hz) frequencies, which may originate in the precentral motor gyrus, is linked to both action perception and production (Gaetz and Cheyne, 2006, Hari and Salmelin, 1997).

1.1.5. Possible role of MN in intentions, social cognition, and language

It has previously been proposed that the frontal-parietal circuit with neurons apparently endowed with mirror properties provides a key mechanism for coding action intention and action understanding (Gallese et al., 2004). In particular, the mirror system has been hypothesized to serve as a matching system for action recognition "through the activation of an internal motor knowledge of an action via the visual or auditory description of the action" (Vanderwert, Fox, Ferrari, 2013). As a result, the observer "knows" the outcome based on his or her own motor representation that helps him or her understand the actor's goal (for a review see Vanderwert, Fox, Ferrari, 2013). Some evidence that the human mirror system is sensitive to an action goal rather than movement itself comes from recent fMRI studies. For example, Gazzola and colleagues had participants observing movies where either a human or a robot arm grasped objects. It was shown that the parieto-frontal mirror system was activated in both conditions despite the differences in the kinematics and visual differences (Gazzola et al., 2007). Additionally, Hamilton and colleagues further addressed

the intention and goal representation using the repetition–suppression paradigm, a technique based on the overall reduction of a physiological response to repeated stimuli. Participants observed a series of movies showing goal-directed actions in a special sequence so that some movies showed novel goals while other showed repeated goals to a previous movement. This showed that the repeated presentation of the same goal caused the suppression of the response in the left intraparietal sulcus (IPS) while this region was not sensitive to the trajectory of the actor's hand (Hamilton et al., 2006). Other fMRI studies looked at whether the activations in this frontal-parietal network are sensitive to action intentions. It was shown that the mirror system was sensitive to intentions, represented in the way the object has been grasped or the context has been executed (Iacoboni et al., 2005). The role of mirror system in the understanding of action intention was further addressed in the fMRI study using the repetition suppression paradigm (Hamilton et al., 2008). The activation in the IFG and the right IPL was suppressed when the outcome of the movement was the same, compared to the condition where the movement was the same but the outcome was different.

Following this proposal of the involvement of mirroring mechanisms in action understanding, the functions of the mirror system in humans have been further expanded to social cognition, imitation and empathy (Rizzolatti & Fabbri-Destro, 2008, Keysers and Fadiga, 2008). More specifically, Rizzolatti and colleagues also suggested that the capacity to associate the visual action with its motor representation leads to the development of higher social abilities, including imitation learning (Rizzolatti et al., 2001). As mentioned earlier, the proposed idea of the role of the mirror system in social cognition is primarily based on the action understanding hypothesis and the fact that the area F5 in monkeys represents a homologue to human Broca's area, which is involved in language production. Rizzolatti and Arbib (Rizzolatti and Arbib, 1998, see also Arbib, 2006) suggested that the mirror system

plays a role in the evolution of language from the early gestural communication system. As a result, it has been speculated the mirror neuron system plays role in language development by transforming phonemes to a motor representation (Fabbri-Destro & Rizzolatti, 2008). Several functional neuroimaging studies showed that some specific cortical regions such as the insula and the adjacent frontal operculum, which are activated during experience of emotions, also exhibit mirror properties (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Jabbi, Swart, & Keysers, 2007; Jackson, Meltzoff, & Decety, 2005; Singer et al., 2004, 2006; van der Gaag, Minderaa, & Keysers, 2007; Wicker et al., 2003). For example, the anterior insula was found to be activated during the first-person experience of disgust and during the observation of emotional images depicting disgust (Wicker et al., 2003). It was further proposed that the mirror mechanism provide unique insights into others' behaviours, both motor and emotional. Evidence for the mirror system involvement in social cognition also comes from clinical research studies, providing indirect EEG index of mirror functioning such as mu rhythm attenuation that was found to be reduced in disorders with known social-cognitive deficits as ASD (Oberman et al., 2005, Theoret et al., 2005, see also Chapter 1, section 1.4 on impairment of the mu rhythm in ASD). This notion has been however criticized on the basis that no direct measure of social cognition has been made in the majority of these studies (Dinstein et al., 2008).

The hypothesis of the involvement of mirror system in language is based, in part, on fMRI studies that showed an overlap of the activation during speech perception and speech production (Callan et al., 2010, Pulvermuller et al., 2006, Wilson et al., 2004). It was proposed that mirroring mechanisms have a causal relationship in speech perception and action understanding (Gallese et al., 2011). This view is supported by the results of studies that have examined activations during the presentation of literal (concrete) and idiomatic

(abstract) speech. In particular, it has been proposed that the fMRI responses to the verb ‘to kick’ and the expression to ‘kick off the year’ imply the same ‘kick’ representation (Aziz-Zadeh, Damasio, 2008). The results of a TMS study by Glenberg and colleagues supported this view by showing a greater modulation of MEPs while participants were reading sentences describing both movement of concrete object or abstract information (Glenberg et al., 2008).

1.1.6. Conclusion

In summary, the abovementioned findings provide evidence for the existence of the mirror system, or a similar matching action observation-execution system, in the human brain. The results of the abovementioned studies provide further indirect evidence for a role of the mirror system in supporting some aspects of social cognition. In particular, the mirror system might provide an implicit mechanism for understanding actions’ intentions and the emotions of other people. Despite this evidence for the involvement of the mirror system in the social cognition, its detailed functioning and the specific role in social cognition and in speech and language development is a highly debated topic.

1.2 Embodied cognition and embodied simulation approaches: application to the perception and experience of action and touch

1.2.1. Embodiment as a concept

Embodiment (or embodied cognition) is enactive approach to cognition, emphasizing how bodily experiences can influence social-cognitive processes and social interactions with the world (Valera et al., 1991, Gallagher, 2001). A particular type of embodiment is described in embodied simulation theories suggested by cognitive scientists (Decety, 1996, Jeannerod, 2001, Gallese, 2007). Based on the experimental evidence, it was argued that many social-cognitive processes are bodily based in a sense that they are influenced by the simulation of sensorimotor processes, most likely through the activation of neural circuitry during both visual and sensorimotor experiences (Svensson & Ziemke, 2004). In this section, I summarise the embodied cognition and embodied simulation approaches, as well as describe main physophysics and neurophysiological findings which are relevant to the experimental body of this thesis –action and touch observation experiences.

1.2.2. Empirical evidence

The idea of the embodied cognition is that many features of social-cognitive processes are related to physical body and bodily actions of an agent (Gallese & Sinigaglia, 2011a). Embodied simulation theory suggests that capacity to understand someone's actions and sensory experiences, as well as to emphasize with others is partially mediated by the neurophysiological simulation mechanism which activates similar neural circuitry during both

observation of experiences of others and our own experiences (Gallese, 2013). The first empirical evidence for this theory comes from mental imagery experiments, suggesting neural and behavioural similarities between actions and motor imagery (for review, see Decety, 1996, 2002). For example, it was found that time to mentally execute action closely corresponds to time which takes to actually perform the same action (Decety and Jeannerod, 1996). Autonomic responses, as well as neural circuitry are found to be largely similar during the experiences of an action and motor imagery (Decety 1996, 2002). Specifically, it was also shown that mental imagery recruits cortical (premotor, motor, SMA) and sub-cortical (basal ganglia, cerebellum) motor regions (Jeannerod, 2001). Interestingly, the activation of these regions was positively correlated with vividness of mental imagery experiences (for a review, see Lorey et al., 2011). Another empirical example of cognitive processes based on embodied simulation is object perception. Several neurophysiological and neuroimaging studies demonstrated that seeing an object selectively recruits the same motor areas that are activated during planning and execution of an action performed with this object (for a review, Gallese & Sinigaglia, 2011b).

Human mirror mechanism, described in Chapter 1, section 1.1, also represents one of the possible experimental accounts for embodied simulation theory (Gallese & Sinigaglia, 2011a). Gallese and Goldman proposed that MNS underpins embodied simulation mechanisms during action observation and even can provide some neurophysiological basis for mind-reading (Gallese and Goldman, 1998). However, it was rightfully noted that mirror mechanism account doesn't provide a plausible explanation how brain can distinguish the observed actions of others' from their own actions (Blackmore et al., 2002).

An important empirical support for simulation theory also comes from studies of action perception and joint action emphasizing the importance of action-perception links for

social interactions (Knoblich and Sebanz, 2006). The evidence for shared mental representation of own and others' actions was obtained in a behavioural study showing that awareness of the presence of another person performing the same task slowed participants responses in a go/no-go task (Sebanz et al., 2003). In a follow-up ERP study, a P300 component analysis revealed stronger inhibition when participants were required not to act because it was another person's turn compared to when were not required to act but were alone (Sebanz et al., 2006). Interestingly, the presence of co-representation of a partner in a joint task was found in children as young as 4 years of age but was not present in younger children, which suggests a relatively late maturation of mental representations of others in children during joint activity (Milward et al., 2014).

1.2.3. Embodied simulation and social cognition

It was previously suggested that the internal reactivation of sensorimotor structures underpinned by embodied simulation, plays a crucial role in social-cognitive and language development (Barsalou, 2003). In fact, neuroimaging evidence demonstrates the activation of cortical and sub-cortical regions involved in motor planning and production during speech perception and production (Hauk et al., 2004, Aziz-Zadeh et al., 2006, see also Chapter 1, section 1.4). The similar logic applies to emotion simulation theories which suggest that empathy and sensations are mediated by the reactivation of internal bodily state in the observer (Neilseen, 2002). Most relevant to this thesis, fMRI evidence demonstrated shared neural circuitries during touch observation and experience (Blackmore et al., 2005, Keysers et al., 2004, see more in Chapter 2, introduction section) and emotion observation and experiences (Wicker et al., 2003, Jabbi et al., 2008). Results of Jabbi and colleagues' study

are particular informative as they also provided evidence that the observation and imagery of disgust activates the same areas (anterior insula) as the experiences, but also some additional areas that allow to distinguish own real emotions from those in the observer (Jabbi et al., 2008).

Further empirical evidence for embodied mechanisms and their role in understanding intentions and emotions of other people and speech perception is also provided in neurophysiological and neuroimaging studies investigating action observation/execution matching mechanism (Chapter 1, section 1.1.4). For example, the fronto-insular cortices were found to be involved in the both the experience and processing of others' negative emotions, pain and empathy (Singer et al., 2004, 2006, Jabbi et al., 2007). As regards to speech processing, some researchers emphasized the role of the motor system in language suggesting that speech perception requires the integration of sensory and motor information (Iacoboni et al., 2008). On the other hand, Hickok and colleagues proposed top-down influence of embodied mechanisms on the acoustic input of the language, further emphasizing that this influence can be very minor (Hickok et al., 2011).

Several fMRI studies have demonstrated relationships between sensorimotor functioning and language processing (Aziz-Zadeh, Wilson, Rizzolatti, & Iacoboni, 2006; Buccino et al., 2005; Hauk, Johnsrude, & Pulvermuller, 2004; Tettamanti et al., 2005). In particular, Hauk and colleagues presented participants with action words referring to different body parts during passive reading task (Hauk et al., 2004). The results showed an overlapping activation of specific body part maps and the linguistic processing of action words which suggests that the meaning of an action word has a correlation in the somatotopic activation of motor cortex (Hauk et al., 2004). In another study, participants observed actions and read phrases related to foot, hand and mouth actions (Aziz-Zadeh et al., 2006). The results showed

congruence between the activations in the premotor cortex underpinned by visually presented actions and by actions described by phrases (Aziz-Zadeh et al., 2006). Additionally, Buccino and colleagues used TMS to show that listening to action-related sentences modulates motor cortex excitability (Buccino et al., 2005). Although the results of these studies demonstrate some relationship between speech processing and sensorimotor functions, they do not show a direct causal link between action observation-execution matching mechanisms and language comprehension.

1.2.4. The embodied self and multisensory integration theory

As regards to tactile experiences, the concept which is closely linked to embodied self and embodiment theory is the multisensory integration theory. In the following part of this section, I briefly describe summarize main findings supporting this theory as they are important for the interpretation of the empirical findings of this thesis, particularly Chapters 2-4.

Multisensory integration theory is based on the idea of a strong interaction between different sensory modalities, such as touch, vision, vestibular system. A psychophysics research demonstrated that perception of touch is affected by visual input, such as seeing touch increases the perceived tactile acuity (Haggard et al., 2007). A follow-up LEP study revealed that seeing the body also decrease the pain induced by infrared laser stimulation (Longo et al., 2009). The subjective rating of the unpleasantness as well as N2/P2 complex of LEP was reduced when participants observed the reflection of participants' hands in the mirror (Longo et al., 2009). Neuroimaging results further support the notion of integration of visual and tactile processes providing evidence that visual areas are involved in social touch

processing (Sereno & Huang 2006, Sereno & Haggard, 2010). In particular, multisensory maps were found in parietal cortex in the areas specialized for eye-movements, hand movements and face-related movements. The majority of these areas contain rough sensory (receptotopic) maps, including a substantial multisensory representation of the lower body and lower visual field next to the face processing area (Sereno & Huang, 2014). The aligned maps of tactile and near-face visual stimuli were also found at the highest level of human association cortex, in the superior part of the postcentral sulcus (Sereno & Huang, 2006). It was further revealed that the multisensory area in posterior parietal cortex is also somatotopically organized suggesting that the precise mapping of multisensory face and body information occurs in this area (Huang et al., 2012).

There is more recent evidence for multisensory theory showing that the integration of visual and tactile information is enhanced when stimuli of different modalities are in the same location (Longo et al., 2012). In this psychophysics and ERP study, the mirror box technique was used to manipulate the congruence of visual and tactile information about which finger on right or left hand was being touched (Longo et al., 2012). The results showed that congruent and incongruent conditions influenced judgments on the location of touch. Additionally, N2 component showed a reduction while P300 component demonstrated an enhancement for visual-tactile events on both right and left hands. Additionally, a recent study also investigated an interaction between vestibular stimulation and tactile systems (Ferre et al., 2013). The results revealed that galvanic vestibular stimulation increased tactile sensitivity suggesting the link between vestibular and tactile processes.

Rubber hand illusion task was used as experimental paradigm to control manipulation of the perceived body, or body ownership (see Tsakiris, 2010, for a review). Using this paradigm, it was shown that participants who experienced rubber hand illusion perceived

their hand more similar to a rubber hand than the participants who did not experience this illusion suggesting that the sense of body ownership had an impact on the perceived visual similarities (Longo et al., 2008). Interestingly, the phenomenon of rubber hand illusion did not occur during asynchronous tactile stimulation, when there was no matching between vision and touch (Tsakiris and Haggard, 2005). The multisensory theory also suggests the embodied sense of self includes several distinguishable components, which include the sense of body ownership and body agency (Longo et al., 2008). A recent neuroimaging study disentangles body ownership (feeling your own body) and sense of agency which is linked to ability to perform voluntary actions (Tsakiris et al., 2011). In particular, the results showed that while body ownership involved the activation of baseline brain activity, so called default mode networks, the sense of agency is linked to premotor and parietal areas which are required for motor planning (Tsakiris et al., 2011).

1.2.5. Conclusion

In sum, both embodiment and embodied simulation theories are supported by a variety of psychophysics and neurophysiological empirical evidence. Additionally, the multisensory integration theory highlights the importance to consider the multisensory nature of the embodied self and sensory experiences suggesting the integration between different sensory modalities, in particularly between vision and touch. The empirical evidence discussed in this section also includes studies on action and touch observation which are reviewed in detail in the experimental chapters of this thesis (Chapter 2-3, introduction sections).

1.3 Social brain development in infancy and childhood in different domains: tactile perception and speech perception and human versus non-human processing

1.3.1. General neuroanatomical development

Human brain development is the process that begins early in gestation (Archiron and Archiron, 1991) and is in part modulated by genetic factors (Hayakawa et al., 2005). More specifically, the first part of gestation corresponds to brain vesicles differentiation and neurogenesis. The second part includes the growth of the cerebral hemispheres as well as gyral and sulci formation (Ehna-Ravazi and Sonigo, 2003). The early tracks of postnatal infants' development were shown with diffusion tensor imaging (DTI) technique which allows determining tissue integrity and mapping the fiber tracts orientation in newborn and young infants and children (Shimony et al., 1999, Kubicki et al., 2002, for a recent review, see Qiu et al., 2015). These studies reported the decrease in apparent diffusion coefficient in both gray matter and white matter, while fractional anisotropy (FA) which indicates axon density and myelination increases with gestational age in infants, especially in white matter, and then continues to increase from early childhood into adulthood (Mukherjee et al., 2001, Engelbrecht et al., 2002). DTI studies also indicate slow white matter maturation in children from 5 years of age into adulthood which was reflected in changes in white matter density and organization (Snook et al., 2005). More specifically, another study examining the overall development of white matter pathways in typically developing children from 6 years of age, reported the positive correlation of fractional anisotropy, an index of white matter development, with age in prefrontal cortex, in basal ganglia, thalamus and cortical-spinal and

cortical-thalamic tracks extending from sensory-motor regions (Barnea-Goraly et al., 2005). Results from longitudinal study of subjects aged from 5 to 32 years suggest the continuing maturation of white matter into adulthood (Lebel & Beaulieu, 2011). More specifically, according to the results of this study, the white matter volume increases with age, while the gray matter decreases, thus leading to no change in the total brain volume. Additionally, FA increased for all fiber tracts but most between-subject differences disappeared in early adolescence apart for associative fibers in fronto-occipital tracts which continued to show FA increase in older groups (Lebel & Beaulieu, 2011).

During the first few years of life, gray matter and the limbic fibers also show a slow increase in FA and decrease in mean diffusion (Oiu et al., 2015). Despite the continuing development of both gray and white matter into adulthood, it was suggested that human brain in neonates already has neural architecture that provides foundation for effective information processing which most intensively develops in the first two years of life (Yap et al., 2011). For example, the infant brain already shows a structural inter-hemispheric asymmetry with more structural efficiency in the left hemisphere than in the right. It was suggested that this structural asymmetry might be important for the foundation of the development of both language and sensory-motor functions in early childhood (Ratnarajah et al., 2013).

Positron-emission tomography (PET) and MRI scans have been also used to study further development of cortical specialization, however due to invasive nature of PET these studies have been restricted to infants and children with clinical symptoms. The results showed that synaptogenesis starts at the same time as other regions in prefrontal cortex, however it starts more slowly and doesn't finish until the second year of life (Huttenlocher et al., 1982). Using PET, it was also shown that there is a rise in glucose metabolism after the first year of life peaking at approximately 4-5 years of life (for a review, see Johnson, 2001).

Additionally, there is some evidence that myelination in some cortical areas continues well into later childhood and adulthood. For example, by using MRI, Sowell and colleagues showed 12 % decrease in a gray matter in anterior cingulate cortex which was attributed to an increase in myelination in children from 7 years of age, compared to older participants (Sowell et al., 2003). More specific investigation of the trajectory of gray matter throughout development showed that gray matter has an inverted U shape of developmental trajectory (Giedd and Rapoport, 2010). Interestingly, the age of the peak of gray matter density is the earliest in the primary somatosensory cortex and latest in higher-order association areas such as dorsolateral prefrontal cortex and superior temporal gyrus (Giedd and Rapoport, 2010).

1.3.2. Social-cognitive functional development: sensorimotor functioning and face processing

Social-cognitive functional development has been studied using both behavioural and neuroimaging and neurophysiological methods in young infants and children. Mark Johnson first described two main theories of functional development include maturational theory and the interactive specialization theory of neural development (Johnson, 2001). Maturational theory relates the neuroanatomical maturation in specific regions to the development of the emerged sensory-motor and cognitive functions. On the other hand, the interactive specialization approach assumes that it is the development of inter-region interaction that triggers neurofunctional development (Johnson, 2001). Majority of behavioural and neurophysiological research of social-cognitive development in infancy and later childhood has been focused so far on face processing mechanisms (Halit et al., 2004, de Haan et al., 2002, Taylor et al., 2004) and sensorimotor functions, including a mirror functioning

(Marshall & Meltzoff, 2011, Vanderwert, Fox, & Ferrari, 2013, Cuevas et al., 2014, see more on the development of mirror functioning in Chapter 3). Sensorimotor functions, including action-perception coupling, develop intensively in infancy, most likely due to intensive increase of sensorimotor experience (Cook et al., 2014). It was shown that cortical thinning proceeds in a back to front direction and occurs first most intensively from birth till 2 years of age in the sensorimotor areas, followed by association areas and lastly by higher-order cortical areas, such as the prefrontal cortex and the posterior parietal cortex (Gilmore et al., 2011). Additionally, the results of a recent MEG study demonstrated that the pattern of functional organization changes in sensorimotor cortex around 1 year of life (Berchicci et al., 2015). In this study, the authors used synchronization likelihood to characterize the functional connectivity and segregation properties of sensorimotor network in five different age groups: two groups of infants (3-5 months, 6-12 moths), two groups of children (2 years and 3-5 years) and adults. The results showed that all functional measures remained unchanged during infancy, but demonstrated an increase of both integration and segregation measures from childhood to adulthood. Thus these results are in line with functional specialization hypothesis of neurofunctional development, demonstrating that functional properties of sensorimotor cortex are modulated by maturation (Berchicci et al., 2015).

As regards to the development of a specific aspect of social processing, face processing mechanisms, the "face sensitive" N170 component, which neural generators have been localized to the right superior temporal sulcus, demonstrates a larger amplitude and longer latency in the response to upright compared to inverted faces in adults (Johnson et al., 2005). Infants as young as 6 months of age exhibit a comparable ERP component (N290) which was shown to have the same neural generators, however this component in infants, and similar more adult-like (N170) component in older children, doesn't show an inversion effect

in infants and children until 8-11 years of life (Taylor et al., 2004). Additionally, the results of a recent neuroimaging study examining progressive and regressive changes in specialization of face processing in children from 5- to 11- years of age, suggest that some regions has been already specialized for face processing at 5 years of age, but other regions which are not specific to face processing were also activated (Joseph, Gathers, & Bhatt, 2011). The results of this study demonstrate dynamic interactions between cortical regions and involvement of different regions at different ages in face processing and therefore, are more in line with interactive specialization account of neurofunctional development (Joseph, Gathers, & Bhatt, 2011). Taken together, these findings suggest that face processing follows a certain developmental trajectory. Although basic abilities to encode faces are present infants, infant cortical face processing is broader and less tuned than that in adults, and gradually becomes more specific to upright faces in later childhood.

1.3.3. Tactile and speech perception development in infancy

Touch is one of sensory functions that develop earliest in gestation (Hooker, 1952, Arabin et al., 1996). Similar to tactile processing, it has been shown that auditory speech preference is already present in newborn infants (Vouloumanos and Werker, 2007). Since not much literature on social-cognitive typical development in speech and tactile domains is present in older children, in this section I briefly review the literature on the development of tactile perception and auditory speech perception in infants.

Physical touch in infancy is not just a bodily sense but a form of early social interaction. Tactile perception is developing along with early development of the social brain, as a part of bodily self and self-other distinction mechanisms, which is primed during

gestation (Strumia, 2005). In fact, it has been proposed that gentle touch expresses more emotion than that communicated via speech and conveys more genuine intention or meaning during social communication (Kaitz et al., 1992, Burgoon, 1991, Burgoon et al., 1992). It has been shown that responses to gentle touch of fetuses occur before the specialized mechanoreceptors are developed (Humphrey, 1966). The results of fNIRS study showed that somatosensory cortex of preterm neonates was activated by painful tactile stimuli, implying that the conscious perception of touch is fully developed by birth and even earlier in gestation (Bartocci et al., 2006). Majority of the literature on the development of tactile perception in infancy has been focused on maternal touch during maternal-infant interactions in full-term and preterm infants (Field, 1984, Stack & Muir, 1990). However there is also some research into infant touch which represents an important modality of communication for an infant. For example, in a study by Moszkowski and Stack (2007), infant touch was found to occur 85% of the time during brief interaction periods and also varied dependent on maternal emotional availability. Maternal touch has been found to soothe, arouse, and elicit specific infant behaviours during face-to-face interactions (Stack, 2004), indicating that touch maybe be used to serve different functions during dyadic interactions (Beebe, 2006; Jean & Stack, 2009; Stack, 2010). Tactile stimulation and massage therapy has been proposed to be a promising tool for the stimulation of social-cognitive development in preterm infants (for a review, see Pepino & Mezzacappa, 2015). It was shown that the activation of prefrontal cortex during pleasant touch is associated with the cortical tactile reward system in adults (Kida & Shinohara, 2013). The results of a recent fNIRS study demonstrated that gentle touch activates anterior prefrontal cortex in 10 months old infants, but this activation was not present in 3- and 6- month old infants suggesting the maturation of tactile affective systems in the first year of life (Kida & Shinohara, 2013).

Despite a very early maturation of tactile processes, some more complex features of tactile perception continue to develop until later childhood. For example, Begum and colleagues found that 4-year-olds demonstrate a deficit in ability to locate tactile stimuli when they did not have sight of hand posture, suggesting that touch is located in an external reference frame by this age (Begum et al., 2014). Additionally, when visual information about current hand posture was available, tactile localization performance was impaired in this age group when the children's hands were uncrossed, which may be due to an early difficulty with integrating visual representations of the hand within the body schema (Begum et al., 2014). The results of cross-sectional behavioral study of participants from 6- to 16- years of age suggested that despite the fact that tactile acuity was affected by a fingertip size in children as in adults, tactile acuity improved with age in tactile grating orientation task (Peters and Goldreich, 2013).

Similarly to tactile perception, infants show an early bias to speech as opposed to non-speech (Vouloumanos and Werker, 2007). In this study, it was shown that newborn infants change their sucking pattern, with higher sucking amplitudes as response to listening speech, which provides support for the idea that the preference for speech over non-speech is innate (Vouloumanos and Werker, 2007). Research has revealed that human fetuses are able to discriminate between their mother’s voice and that of another female in the womb (Kisilevsky et al., 2003). Infants have neural networks which are sensitive to mother's voice which are evident before birth (Kisilevsky et al., 2003). It was shown that before word production, infants can recognize familiar words (Halle & De Boysson-Bardies, 1996; Harris et al., 1995), discriminate their native language from other languages (Bosch & Sebastián-Gallés, 1997, Nazzi et al., 2000) and distinguish differences between different phonetic parts such as consonants (Halle & De Boysson-Bardies, 1996) and vowels (Polka & Bohn, 2003). In terms

of brain activity, it was found that left-lateralized brain regions including the superior temporal gyrus are activated during speech perception in infancy (Dehaene-Lambertz, 2000, Dehaene-Lambertz et al., 2002, Minagawa-Kawai et al., 2010), however several other studies report a bilateral activation of the temporal cortex in response to speech (Dehaene-Lambertz et al., 2006, Kotilahti et al., 2010). It has been proposed that specialized lateralization of speech processing brain areas is not fully developed in infancy and continues to develop until later childhood (for a review, see Minagawa-Kawai et al., 2011). In line with this notion, the results of an fMRI study suggested that left-lateralization of language occurs around 5 years of age (Balsamo et al., 2006).

1.3.4. Conclusion

In sum, neuroanatomical findings suggest the ongoing cortical and sub-cortical maturation in early infancy and until later childhood into adulthood. In general, social-cognitive development is linked to both neuroanatomical maturation of specific regions and specialization of cortical regions formed by inter-connections and interactions between different cortical regions. Although the aspects of social-cognitive functioning which are relevant to the current thesis are present and developing intensively in early infancy (sensorimotor functioning, face processing, tactile and speech perception), their maturation continues until later childhood and adolescence.

1.4 Social and speech processing in children with ASD

1.4.1. Introduction

The neurophysiological evidence demonstrating dysfunctional mirror mechanisms in individuals with ASD (section 1.3.2) opened up a possibility to further look at the nature of these mechanisms, as well as other social processing deficits in ASD. ASD is a heterogeneous disorder —an individual's degree of impairment varies widely in the core areas of language, cognition and social-cognitive functioning. Due to the increased prevalence of ASD over past several years, prevalence of social and language dysfunctions among other symptoms in ASD and to the high cost of the treatment of these symptoms to society (DiCicco-Bloom et al., 2006; Fombonne, 2004; Knapp, Romeo & Beecham, 2009), the neurophysiological mechanisms underlying social versus non-social processing in ASD have been widely investigated. The 'social motivation' theory suggests that an impaired social reward system might underlie the reduced social attention and social processing deficits, which includes processing faces, human actions, and speech (Abrams et al., 2013). In this section, I will present the main neurophysiological research on social processing in children and adults with autism which includes the processing of static and dynamic social stimuli, human actions, and auditory speech and language.

1.4.2. Social processing in ASD – example of face processing and biological motion

Several research groups have used neuroimaging and electrophysiological techniques to investigate brain networks and functions associated with the processing of social stimuli in

autism. Such stimuli included socially relevant static and dynamic stimuli, such as perception of people's faces and eye-gaze, biological motion, action perception and understanding and speech. Over the past two decades, convincing evidence has revealed atypical processing of faces, including facial expressions and emotions in autism (e.g. Dawson et al., 2002; Dawson et al., 2004; Pelphrey, Morris, McCarthy, & LaBar, 2007; Pierce, Müller, Ambrose, Allen, & Courchesne, 2001; Pierce & Redcay, 2008; Jemel, Mottron, & Dawson, 2006; Schultz, 2005, Webb et al., 2006; Webb et al., 2011) and eye gaze (e.g. Grice et al., 2005; Pelphrey, Morris, & McCarthy, 2005). For example, previous ERP studies showed that young children with autism failed to show differential responses to familiar versus unfamiliar faces, however they demonstrated an enhanced response to objects, in comparison with typically developing children (Dawson et al., 2002, Webb et al., 2006). Another line of research suggests that individuals with autism do not have an absolute deficit of face processing but demonstrate a particular way of processing faces and non-social objects, compared with neurotypical controls (Lopez et al., 2004, Behrmann et al., 2006, Mottron et al., 2006, see also Jemel et al., 2006, for a review). Specifically, Jemel and colleagues argued that individuals with autism exhibit a preference for processing local features of faces and non-social objects as opposed to an impairment of integrating global features in faces which was suggested earlier (Jemel et al., 2006, McPartland et al., 2004, Schultz, 2005). Additionally, an fMRI study revealed similar activity in fusiform gyrus in response to their mother's face and the faces of familiar or unfamiliar children, but significantly less activity in response to strangers' faces in school-aged children with ASD (Pierce & Redcay, 2008). Another fMRI study investigated eye-gaze in adults with ASD compared to controls (Pelphrey et al., 2005). In this study, participants watched as a virtual actor looked towards someone who appeared in her visual field in the congruent task, while in the incongruent task this actor looked away at an empty space. The

results revealed that the same regions including suprerior temporal sulcus (STS) were activated in controls and adults with ASD, however this activation was similar for congruent and incongruent tasks in adults with ASD. Altogether, these findings demonstrated differences in processing eye-gaze and facial features in individuals with ASD compared to controls. However, there is still a debate whether social processing deficits in autism are driven either by a decreased attention to faces and other social stimuli or an enhanced processing of non-social stimuli and local features in faces as opposed to global features (MCleery et al., 2011, Mottron et al., 2006, Jemel et al., 2006).

In addition to differential processing of facial features and eye-gaze, several previous neuroimaging studies have reported atypical processing of biological motion in adults with autism (e.g. Castelli, et al., 2002, Freitag et al., 2008, Herrington et al., 2007). More specifically, Castelli and colleagues presented adults with ASD and control participants with the animations of triangles, which either moved in a random or in a goal-directed way, or implied social interactions with each other. This showed that the ASD group made more mistakes describing triangle movements in the third condition which required the judgment about the social interactions. Interestingly, Freitag and colleagues revealed intact biological motion recognition in adults and adolescents with ASD but longer reaction times for biological and scrambled motion recognition, compared with neurotypical controls (Freitag et al., 2008). Also, the neuroimaging results revealed less activity in the so-called 'mentalizing' neural network which included the STS, the temporal poles and the medial prefrontal cortex, in the ASD group relative to the comparison group (Castelli et al., 2002). Additionally, the functional connectivity of extrastriate cortex with the STS at the temporo-parietal junction was reduced in the autism group (Castelli et al., 2002). These results further suggest that

individuals with ASD demonstrate an atypical biological motion processing as well 'mentalizing' neural circuitry.

Another research group presented adolescents with ASD with biological motion and found reduced activity over frontal and parietal regions, as well as over the posterior STS in adolescents with ASD compared to typically developing participants (Koldewyn et al., 2010). In addition, in a recent fMRI study Kaiser and colleagues looked at biological motion processing in children with ASD, their unaffected siblings and typically developing children (Kaiser et al., 2010b). Three possible neural signatures of ASD were identified: 'state activity', that is related to the state of having a disruption of an activity which characterized children with ASD; 'trait activity', which was reflected in shared activations in children with ASD and their unaffected siblings; 'compensatory activity', which was unique to unaffected siblings (Kaiser et al., 2010b).These findings provide some evidence for the ASD neuroendophenotype for processing biological motion and open up new possibilities in the future research with children with ASD and their unaffected siblings.

1.4.3. Mirror functioning and action processing in ASD

Several research groups focused on the investigation of action mirroring in autism (e.g. Bernier et al., 2007, Martineau, et al., 2008, Oberman et al., 2005, see also Hamilton, 2013, for a review). The hypothesis of the dysfunction of mirror functioning in autism was primarily based on the proposed role of the mirror functioning in the social cognition (see Chapter 1, section 1.2.2).

Studies utilizing neuroimaging techniques confirmed the impaired mirror functioning in individuals with ASD (Oberman et al., 2008, Dapretto et al., 2006, Bastiaansen et al., 2011, Martineau et al., 2010). More specifically, fMRI study reported a diminished activity in the IFG, a region that is included in the human mirror system, in 12 year old children with ASD (Dapretto et al., 2006). Additionally, it was found that activity in IFG was negatively correlated with children's scores on the social subscales of Autistic Diagnostic Observation Scales-Generic (ADOS-G) and the Autism Diagnostic Interview –Revised (ADI-R). In contrast, Martineau and colleagues found an increased inferior frontal gyrus activity during the observation of hand movements compared to neurotypical controls (Martineau et al., 2010). In line with this, a recent fMRI study reported an increased activation of left inferior frontal gyrus and other areas of mirroring networks which were involved in inferring the intentions of others in children with ASD (Libero et al., 2014).

In addition, another fMRI study showed that the inferior frontal gyrus activity during the observation of dynamic facial expressions was positively correlated with the age of ASD participants (Bastiaansen et al., 2011). Interestingly, the age-associated increase in neural activity was correlated with improvements of social-cognitive functioning and changes in the eye-gaze. These findings suggest that mirror functioning might improve with age in ASD, and that these changes are accompanied by changes in eye-gaze and improvement in social functioning. Additionally, Grezes and colleagues used fMRI during the perception of fearful and neutral gestures (Grezes et al., 2009). This showed that individuals with autism failed to activate the amygdala, inferior frontal gyrus and premotor areas during the observation of gestures expressing fear. This failure to 'grasp the affective meaning of an action' was interpreted as the core mechanism contributing to social-cognitive impairments in autism (Grezes et al., 2009).

These neuroimaging findings are in line with the findings of studies utilizing TMS (Theoret et al., 2005, Enticott et al., 2012). These studies showed a reduced modulation of primary motor cortex (M1) excitability during the observation of both meaningless movements and grasping actions in individuals with ASD. These results further suggest that the system matching action observation and execution is impaired in ASD. In addition, several EEG studies reported a lack of suppression of a sensory-motor mu rhythm in children and adults with ASD which is an electrophysiological index of the human mirror system (Oberman et al., 2005, 2008, Bernier et al., 2007). More specifically, Oberman and colleagues reported the lack of the mu suppression in children with ASD compared to controls in the condition when the participants watched a video of a moving hand, but not in the condition when they watched a video of a bouncing ball (Oberman et al., 2005). The same group also reported the presence of mu suppression in 8- to 12- year old children with ASD but only in the conditions where hand actions were performed by familiar individuals (Oberman et al., 2008). A more recent study provided a more thorough examination of age-related differences in the mu suppression, on a sample of over 50 individuals with ASD from 6 to 17 years of age pooled together from the previously published studies (Oberman et al., 2013). A significant correlation was found between age and mu suppression for both individuals with ASD and neurotypical controls. Additionally, the strength of this correlation during action observation did not differ between the groups. Therefore, these results provide some evidence that goes against the abovementioned suggestion that mirror system can improve with age (Oberman et al., 2013).

It is worth mentioning that there is some evidence from the studies utilizing fMRI (Dinstein et al., 2010, see also Hamilton et al., 2013, for a review), EMG (Pascolo & Cattarinussi, 2012) and EEG techniques (Fan et al., 2010) that shows an intact mirror system

in ASD. More specifically, Fan and colleagues found that individuals with ASD exhibited a stronger mu suppression when watching a moving hand compared to watching a video of a moving dot, similarly to controls (Fan et al., 2010). Similarly, Dinstein and colleagues found no difference in a typical movement selective adaption response in repetition suppression paradigms between individuals with ASD and controls (Dinstein et al., 2010). It is worth noting, that despite these few studies, the majority of the abovementioned literature suggests the impairment of some aspects of mirror functioning in individuals with ASD (for a review, see Becchio & Castiello, 2012). However, taking these mixed findings, it might be important to take further into account the heterogeneity and a more complex clinical picture of ASD in the future neurophysiological research.

1.4.4. Speech and non-speech processing in ASD

Thorough investigation of speech processing mechanisms in ASD is important to provide a deeper insight and understanding of social and non-social processing mechanisms in ASD relative to typical development. Speech represents a good model for studying neurophysiological mechanisms of social and non-social processing, especially in case when speech and non-speech stimuli are semantically simple, thus an additional component related to semantic processing is absent. Additionally, a more complete picture of the nature of the neural mechanisms of speech over non-speech discrimination is crucial for our further understanding of typical and atypical language development. It has previously been suggested that language and social functioning mechanisms are mediated by shared brain mechanisms and networks, including the superior temporal sulcus (STS) which has been found to be neuroanatomically and neurofunctionally impaired in autism (Redcay, 2008, Boddaert et al.,

2004b). Interestingly, previous neuroimaging studies showed that STS is also a part of the neural system supporting action recognition and biological action processing, such as movement of bodies or specific body parts (Oram and Perrett, 1994, Blake and Shiffrar, 2007, Adolphs, 2009, Jellema et al., 2004, Barraclough et al., 2006, Vangeneugden et al., 2009). Additionally, there is some recent evidence for the increased connectivity during speech comprehension tasks between a portion of Broca's area and the inferior frontal gyrus and other parts of frontal-parietal network involved in human mirror system (Smirnov et al., 2014) which is found to be dysfunctional in ASD (Bastiaansen et al., 2011, Dapretto et al., 2006, Martineau et al., 2010, Honaga et al., 2010). Taken together, these findings allow us to suggest a possible link between deficient speech and language development and atypical social processing, including biological action processing and mirror functioning in ASD. In this section, I further present the main behavioural and neurophysiological findings in speech versus non-speech processing, in adults and children with ASD.

Previous behavioural research demonstrated that unlike typically developing children, children with ASD do not demonstrate a preference for their mother's voice (Klin et al., 1991). In this study, the authors used audio feedback with either mother's speech or superimposed noises in a busy canteen. In contrast to a comparison group of typically developing children, who showed a preference for their mother's voice, children with ASD exhibited a preference for alternative sounds, or did not show any preference for either sounds. These findings were replicated by a study by Kuhl and colleagues in 2- to 4- year old children, who used a speech spoken by a woman who wasn't a child's mother and compared their responses with more closely matched non-speech analogue stimuli (Kuhl et al., 2005). It was suggested that this null preference to speech sounds is associated more broadly with social attention and orienting deficits (Dawson et al., 2004, Dawson et al., 2012, Klin et al.,

2009) which causes the increased preference to non-social stimuli over faces, and the diminished processing of human actions and speech (Kuhl et al., 2005, see also Chapter 1, sections 1.6.1 and section 1.6.2.). In line with this view, in a follow-up study Kuhl and colleagues found that variability in social orienting was associated with children's speech discrimination skills (Kuhl et al., 2005). In this study, a standard 'mismatch negativity' (MMN) paradigm was used, which most likely cognitively reflects the comparison of a rare deviant stimuli and frequent standard stimuli which are stored in working memory (Naataneen et al., 2007, May & Tiititen, 2010). Children were divided into sub-groups based on whether or not they exhibited a preference to non-speech over speech. This demonstrated that children with autism who exhibited a behavioural preference for non-speech over speech sounds failed to exhibit neural mismatch negativity (MMN) responses which indicated phonetic stimulus discrimination, whereas children with ASD who exhibited a behavioural preference for speech exhibited the same MMN responses as typically developing children.

Several electrophysiological and neuroimaging studies contributed to the behavioural findings by further investigating speech discrimination and processing abnormalities in children and adults with ASD. Electrophysiological research investigated sound discrimination and orienting to speech mostly by implementing oddball MMN ERP paradigms (Ceponiene et al., 2003, Kuhl et al., 2005, Lepisto et al., 2005, Lepisto et al., 2007, Lepisto et al., 2006, Kujala et al., 2013). For example, Ceponiene and colleagues utilized the MMN paradigm in order to examine the neural mechanisms of attentional orienting to both speech and non-speech stimulus changes in children with autism (Ceponiene et al., 2003). This showed that while the control group exhibited attentional orienting responses, reflected in the amplitude of P3a component, to rarely presented frequency contrast stimuli in speech and non-speech conditions, the children with autism failed to exhibit attentional orienting

responses during the speech contrast conditions (Ceponiene et al., 2003). These results further suggest that impairments in the neural systems that mediate involuntary orienting to changes in sounds may be relatively specific to the processing of speech stimuli in children with ASD. Findings of other studies also showed a reduced P3a attentional orienting responses, as well as smaller MMN component amplitudes in response to pitch changes in speech sounds in children with autism, relative to controls (Kujala, Lepisto, & Naatanen, 2013; Lepisto et al., 2005; Lepisto et al., 2006). Specifically, Kujala and colleagues examined the MMN response to changes in vocal prosody in adults with Asperger's syndrome, a syndrome which is included under a single 'umbrella' term ASD (Kujala et al., 2005, American Psychiatric Association, 2013). In this study, participants were required to identify an infrequently presented word spoken in an emotional tone from the same word spoken in a neutral voice. It was found that adults with Asperger's syndrome exhibited delayed MMN latencies and smaller MMN amplitudes to emotional deviant words and also showed a different scalp distribution, in particular in the right hemisphere (Kujala et al., 2005). Another MEG study reported longer MMN latencies to infrequent changes in vowel or consonant stimuli in children with Asperger's syndrome compared to typically developing children (Kasai et al., 2005).

A more recent study investigating attention orienting to speech sounds in individuals with ASD reported a reduced P3a amplitude to speech changes as well as an increased amplitude of the P3a component to non-speech sound changes in adults with Asperger's syndrome (Lepisto et al., 2007). Importantly, this involuntary orienting was more impaired in relation to speech than to non-speech sounds, as reflected in the amplitude of P3a response (Lepisto et al., 2005). Other studies have also identified a reduced amplitude of the P3b component which reflects classification of a novel speech sound embedded in the stream of

standard speech sounds (Courchesne et al., 1984, Courchesne et al., 1985). In addition to the differences in cognitive components, which reflect classification and cognitive processing of stimuli (P3a, P3b, MMN), the differences were also observed in early sensory evoked potential components (P1, N1) in response to speech sounds. More specifically, smaller P1 amplitudes as well as delayed P1 latencies to speech stimuli were reported in individuals with ASD relative to controls (Lepisto et al., 2005, Russo et al., 2009). Additionally, another EEG study suggested atypical neural responses to affective speech, reflected in the amplitudes of N1 component (Korpilahti et al., 2007, see also O'Connor, 2012, for a review).

In a more recent study, Whitehouse and Bishop utilised a variation of the MMN paradigm where they presented rare novel speech stimuli within a stream of repetitive non-speech stimuli and also rare novel non-speech stimuli in the context of a repetitive stream of speech stimuli (Whitehouse & Bishop, 2008). This revealed that the P3a responses were larger in children with autism relative to controls in the repetitive non-speech condition (rare speech sound), whereas their P3a responses were smaller relative to controls in the repetitive speech condition (rare non-speech sound). Interestingly, these group differences were not observed in an active condition in which children were required to pay attention to the sounds. These results suggest that the detection of speech sounds is not universally impaired in children with ASD. Instead, these results suggest that these children may "turn off" their discriminative and attentional orienting responses when exposed to a repetitive stream of speech (Whitehouse & Bishop, 2008). Therefore, additional research might be needed to establish whether the diminished P3a responses to deviant speech sounds in the abovementioned ERP studies (Ceponiene et al., 2003, Kuhl et al., 2005, Lepisto et al., 2005, Lepisto et al., 2007, Lepisto et al., 2006, Kujala et al., 2013) might reflect a

reduced/switching attention to novel speech stimuli rather than just representing a "turn off" attention response to a repetitive stream of standard speech stimuli.

It was also found that speech processing in ASD elicited differences at later cognitive stages of processing reflected in the amplitude of the N400 component (Lepisto et al., 2005, Kujala et al., 2013). More specifically, N400 responses were found to be diminished in ASD and these differences were not observed for a non-speech tone (Lepisto et al., 2005, Lepisto et al., 2006). Additionally, McCleery and colleagues examined N400 responses to matched and mismatched auditory visual stimuli in typically developing children and children with ASD (McCleery et al., 2010). This showed that, unlike their typically developing peers, children with ASD did not elicit larger N400 to congruent compared to incongruent word-picture stimuli (McCleery et al., 2010). It was suggested that the smaller amplitude of N400 in ASD might reflect an atypical integration of semantic information in the speech context (for a review, see O'Connor, 2012).

In addition to the electrophysiological findings, recent fMRI studies revealed a reduced activity in the left temporal cortex (Eyler et al., 2012) as well as greater right temporal hemispheric activation in response to speech sounds in children with ASD (Eyler et al., 2012, Redcay & Courchesne, 2008). A rightward hemispheric asymmetry in auditory association areas sub-serving language was observed in individuals with ASD (Gage et al., 2009). It is worth noting though that literature on the hemispheric lateralization of speech processing in ASD is mixed. For example, two other neuroimaging studies reported an increased activation in the left hemisphere in temporal regions in children with ASD during semantic task (Harris et al., 2006) and song processing (Lai et al., 2012). Additionally, it was shown that toddlers with ASD have a weaker inter-hemispheric connectivity (Dinstein et al., 2010). Interestingly, a recent study fMRI study revealed the under-connectivity between right

posterior STS, associated with speech prosody processing, and brain areas associated with emotion and reward processing, including the amygdala, the orbitofrontal and prefrontal cortices, in children with ASD (Abrams et al., 2013). Overall, these findings support the social motivation theory of ASD which suggests that impaired reward processing might underlie diminished social attention and atypical processing of socially relevant stimuli, such as faces, human actions and speech in autism (Abrams et al., 2013, Dawson et al., 2012).

1.4.5. Conclusion

In summary, the current findings demonstrate the neurophysiological evidence for deficient speech and social processing in ASD. More specifically, ASD might be characterised by atypical processing of biological actions, as well as a dysfunctional mirror system. Finally, the outlined literature presents neurophysiological evidence for speech processing dysfunctions in ASD, specifically a diminished response and impaired classification of auditory speech sounds, as well as behavioural preference for non-speech and atypical processing of non-speech sounds. Further neurophysiological research needs to be carried out in order to provide deeper insights into the nature of the mechanisms of social-cognitive deficits, as well as possible connections and functional meaning of social and speech dysfunctions, in individuals with autism.

1.5 Methodological considerations

For a number of reasons, the EEG technique represents one of the most suitable methods for the study of brain processing in infants and children (de Haan, 2013, Nelson & McCleery, 2008). For example, high-density EEG arrays are relatively quick and easy to put on, which is an important advantage when studying brain functioning in infants and young children. Furthermore, EEG is less sensitive to movement artifacts, compared to MEG technique, which makes it more practical to use in infants and children with neurodevelopmental disorders (de Haan, 2013). Therefore, these features, together with high temporal resolution of EEG, make it the most suitable technique to utilize in ERP and EEG research in Chapters 2-5.

The empirical evidence for embodiment and mirror functioning opens a possibility to conduct studies of infants, in order to investigate the development of observation/execution matching mechanisms in infancy. Specifically, several EEG studies have shown the presence of mu desynchronization during action observation in infants suggesting the development of action mirroring from approximately 8-to-12 months of age (van Elk et al., 2009, Nystrom et al., 2008, Nystrom et al., 2011, Marshall et al., 2011, for review see Vanderwert, Fox, Ferrari, 2013, Cuevas et al., 2014, see more Chapter 4, introduction section). Cuevas and colleagues (Cuevas et al., 2014) discussed a few methodological considerations for developmental EEG and ERP research of mu oscillations which will be briefly discussed in this section, as they are relevant for the experimental studies in Chapters 3-4.

First, the inclusion of baseline condition is very important when looking into sensorimotor rhythm oscillations. The choice of the baseline, or inclusion of multiple baselines, for example, both moving and non-moving baselines, is also important, as it will

increase the interpretability of the data. Second, the authors suggested that it is important to look at different ranges of oscillations, including different ranges of alpha (6-9 Hz, 8-12 Hz) and beta (15-24 Hz) ranges, in different brain areas, in order to get a full picture of the developmental properties of movement-related brain oscillations (Cuevas et al., 2014). The authors also emphasized a particular strength of event-related designs, for which baseline cannot be selected immediately before target videos. Finally, it is important to include both observation and execution conditions, and live observation trials are generally found to be more effective than videos in infants (Cuevas et al., 2014). Most of these considerations were taken into account when designing studies in Chapters 2-4. For example, an event-related design was employed to study touch observation in adults and children in Chapters 2-3. Additionally, tactile stimulation in Chapter 4 was accompanied by live observation of experimenter touching children's hands. Finally, different ranges of oscillations (both alpha and beta rhythms) were explored in children in Chapter 4.

1.6 Outline of Chapters

Having reviewed the relevant literature, I will move on to describe in detail the research carried out as the main object of this thesis, that is the experimental ERP study of human touch versus non-touch observation in adults and children (Chapter 2, Chapter 3), an EEG study of touch processing in adults and children (Chapter 4) and an ERP study of speech and non-speech processing in children with ASD (Chapter 5). Chapter 2 also presents the ERP methodology for both Chapter 2 and Chapter 3. In Chapter 3, I will further assess and discuss children's mechanisms for hand and object touch versus non-touch observation, while Chapter 4 will present the results of the EEG time-frequency analysis of touch processing

mechanisms in adults and children. In Chapter 5, I will present the results and further discuss the ERP correlates of speech versus computerized processing mechanisms in children ASD and typically developing children. Finally, in Chapter 6 (General Discussion) I will summarize the results of all experimental studies and discuss further the limitations of these studies and directions for the future research.

CHAPTER 2:

NEURAL MECHANISMS OF THE OBSERVATION OF HAND AND OBJECT TOUCH

The following chapter is based on the material that has been published in the Journal of Cognitive Social and Affective Neurosciences (first published online in November 2012, doi: 10.1093/scan/nss142). Alterations have been made to the methods and results sections, in order to make it consistent with other chapters.

Streltsova, A. &McCleery, J.P. (2014). "Neural time-course of the observation of human and non-human object touch". Journal of Social Cognitive and Affective Neurosciences, 9(3), 333-341.

Abstract

Recent functional Magnetic Resona nce Imaging (fMRI) studies have reported activation of primary and secondary somatosensory cortices when participants observe another person or object being touched. In the current study, we used event-related potentials (ERPs) to examine the nature and time-course of the neural mechanisms associated with the observation of humans and non-human objects being touched. Participants were presented with short video clips of a human arm or a non-human cylindrical object being touched by an object, compared with an object moving in front of the arms or cylinders without touching them. Touch versus non-touch effects were observed in the amplitudes of the N100 and N250 components, as well as a late slow wave component (500 – 600 ms), measured from electrodes over primary somatosensory cortex. Human versus non-human stimulus effects were reflected in the latencies of the N100, P170, and N250 components recorded over somatosensory cortex, as well as the temporal-parietal visual-perceptual N170 and N250 components. These findings suggest that human and non-human touch observation are associated with somatosensory processing at both an early sensory-perceptual stage and a relatively late cognitive stage, both preceding and following the perceptual encoding of the humanness of stimuli that typically occurs in extrastriate visual areas.

Introduction

Recent functional magnetic resonance imaging (fMRI) studies have demonstrated that observation of another person being touched can activate both primary (SI) and secondary somatosensory (SII) cortices, core brain regions associated with sensation processing. Some studies report similar activations of SI or SII when participants experience touch and when they observe another person or object being touched (Blakemore et al., 2005; Ebisch et al. 2008, 2010; Keysers et al. 2004; Osborn & Derbyshire, 2010; Schaefer et al. 2006, 2009). In a recent review of somatosensory processing in social contexts, Keysers and colleagues concluded that higher stages of somatosensory processing are activated during the observation of touch as well as during the observation of an action or someone experiencing somatic pain (Keysers et al., 2010). They further suggest that this somatosensory activity may be related to visuotactile mirroring mechanisms, where the observation of an action automatically activates portions of corresponding neural circuits in the observer (see e.g., Rizzolatti, Craghiero 2004; Cattaneo & Rizzolatti 2010).

Due to the low temporal resolution of functional Magnetic Resonance Imaging (fMRI), event-related studies utilising electromagnetic imaging measures, such as electroencephalography (EEG) and magnetoencephalography (MEG), are critical for determining the neural time-course of observed touch processing. Three electromagnetic imaging studies have previously examined the time-course of activation of somatosensory cortex during the observation of another person being touched. Pihko and colleagues recorded event-related MEG data while finger taps were delivered to participants' dorsal right hand (touch condition) and when the participants observed an experimenter being touched in a similar manner (observation condition; Pihko et al., 2010). SI was activated during the first

300 ms of tactile stimulation, and similar activations were observed between 300 and 600 ms during the observation of touch. In an earlier event-related EEG study, somatosensory-evoked potentials (SEPs) were measured during the observation of painful and neutral tactile stimulation (Bufalari et al. 2007). The amplitude of the P45 component, the positive-going somatosensory component peaking 45 ms following stimulus onset, was modulated during the observation of both painful and neutral touch. Recently, Martinez-Jauand and colleagues looked at whether the somatosensory activity could be modulated by the observation of bodily experiences. In this event-related EEG study, SEPs were measured when participants viewed a hand penetrated by a needle (Martinez-Jauand et al., 2012). This revealed enhanced amplitudes of the P50 component during the observation of both pain and touch which were associated with increased unpleasant ratings of touch, as well as with high scores on a perspective taking scale. Importantly, only one of these three studies (Pihko et al., 2010) examined the time-course of the observation of touch which was not accompanied by tactile stimulation.

These studies provide initial MEG and EEG/SEP evidence that somatosensory cortex is modulated by the observation of touch. However, the particular time-course of somatosensory cortex activation during human touch observation differed dramatically between studies. In addition, neither study examined the specificity of the activation of somatosensory cortex during the observation of touching humans versus non-human objects. The results of fMRI studies suggest that activation levels in somatosensory regions are similar during the observation of these two types of touch (Keysers et al., 2004, Ebisch et al., 2008, but see also Blakemore et al., 2005). It remains unknown, however, whether or not the time-course of the activation of somatosensory cortex differs when observing humans versus objects being touched.

In the present study, we examine the time-course of somatosensory processing components during the observation of humans versus objects being touched. Previous event-related electromagnetic imaging research on the observation of humans being touched suggests that touch versus non-touch effects would occur at an early sensory processing stage (i.e., within 100 ms) and/or at a much later cognitive stage (i.e., 300 to 600 ms), whereas previous fMRI studies suggest no difference in the levels of activity. Thus, we predict that human and object touch versus non-touch effects would differ in their timing, but not in the level of activity that they evoke.

Methods

Participants

Participants in the final study were 16 undergraduate students (4 males, 12 females) from the University of Birmingham. These participants had a mean age of 21 years (range: 18-26 years). All participants included in the study reported that they were right-handed. Data from three additional participants were excluded from analysis because they produced fewer than 30 trials of viable EEG/ERP data in one or more of the four experimental conditions. All participants reported that they had no history of a neurological or psychiatric disorder, and that they had normal or corrected to normal vision. Informed consent was obtained for all participants prior to participation in the study, in accordance with an ethical protocol approved by the Ethical Review Committee of the University of Birmingham.

Materials

Videos were in .avi format and were recorded using a digital camera with a resolution of 720 x 480 color pixels, and with a frame rate of 29.97 frames/second, positioned 60 cm from the actor or object. The following parameters were used for all of the video recordings: frequency rate: 25 Hz, 75 frames, pixel aspect ratio: 1.067. All video clips were created using Pinnacle Studio 12, and edited down to a length of 25 frames, corresponding to a total duration of approximately 830 ms. All human stimulus video clips presented the right or left palm and forearm of a male or female actor, from an egocentric point of view. All non-human stimulus video clips presented a cylindrical object from either a right or left side orientation. The stimulus set for each condition was comprised of 12 different video clips, 6 videos for each actor or object, for a total of 48 stimuli (see example stimuli in **Figure 2.1**). Each video in the touch condition demonstrated either the left or right palm and forearm of an actor, or an object, and one of three objects (peacock feather, brush, plastic arm massager) approaching the arm or object and subsequently touching it. For the non-touch condition, the videos involved the same object (feather, brush, plastic arm massager), approaching the arm of the person or object and moving in front of it, but without touching it. A pilot stimuli rating was carried on 8 participants (5 males) prior to the experiment, in order to determine whether the videos in touch and non-touch conditions can be easily distinguished. The results showed that 7 out of 8 participants could discriminate the presence of touch in the videos 100 % accurately, while one participant made a mistake with one videoclip (98 % accuracy).

Each video was repeated 6 times, so that 72 trials were presented in total for each condition. The average onset of movement in front of an object or touch of an object or person was measured to be precisely 63 ms after the visual onset of the video for each condition. Finally, four additional video clips that corresponded to each of the four

experimental conditions were modified using a colour editing Pinnacle toolbox, so that they represented arm and objects of different colors. These videos were used as "target" trials (4 % of all video clips) for participant behavioural responses, and were not included in further data analysis.

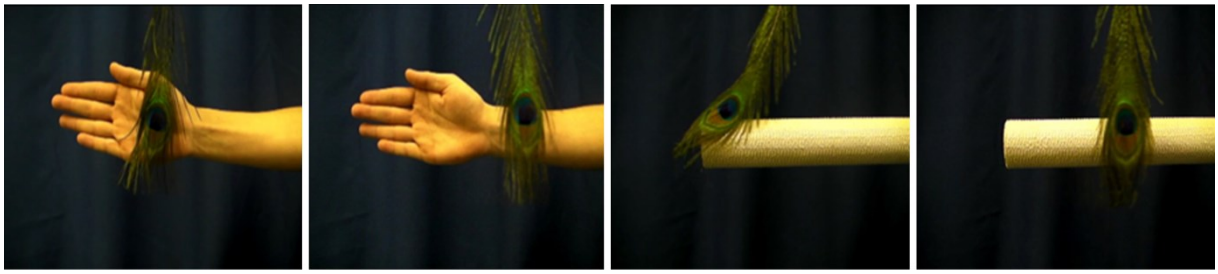

Figure 2.1. Stimuli. Example frames extracted from the video clips in the four experimental conditions: (1) Hand touch (an object moving in front of a male arm and palm and touching it); (2) Hand non-touch (an object moving in front of an arm and palm without touching it); (3) Object touch (an object moving in front of a white roll and touching it); and (4) Object non-touch (an object moving in front of a white roll without touching it).

Experimental procedure

Participants were seated comfortably in an isolated sound-attenuated EEG/ERP testing room in front of the computer stimulus monitor. Participants were asked to watch all of the video clips, and to press a button on a response box when they saw a movie in which the human or object stimulus was an unusual colour (e.g., green hand or green cylinder). To ensure that participants understood which were the target stimuli, they were shown pictures of the video clips with normally coloured human and non-human stimuli alongside pictures of off-colour target stimuli that required a response, prior to initiating the experiment.

The experiment consisted of two separate blocks of trials: observation of human touch and non-touch (HUMAN), and the observation of object touch and non-touch (OBJECT).

During the observation of HUMAN touch, participants were presented with videos showing an arm with an object touching (touch) it or moving in front of it (non-touch). Similarly, during the OBJECT condition, participants were presented with videos showing a cylindrical object with another object either touching it or moving in front of it. In order to prime participants for the experiment, the participant's arm and palm were touched gently with the same touch objects that were presented in the video clips (peacock feather, brush, plastic arm massager). This tactile stimulation was conducted for approximately 6 minutes in total, 3 minutes per arm. The same soft force and medium speed of stimulation was maintained for both hands and across participants. In order to maintain the same velocity of tactile movements, the experimenter counted the rhythm internally. This tactile stimulation priming procedure was also conducted again prior to the second block of ERP trials.

Each ERP observation trial began with a baseline period of 1000 ms, presenting a blank black screen. This was then followed by a central fixation cross, which varied in duration from 800 ms to 1000 ms. Finally, the touch or non-touch video stimulus was presented for 830 ms (25 frames). As described above, the event-related observation stimuli were presented in two separate blocks – HUMAN (human touch and non-touch) and OBJECT (object touch and non-touch). The order of the blocks was randomized across participants. The order of the trials presented within each block was also randomized.

EEG recording and data analysis

EEG data were acquired using a 128-channel Hydrocel Geodesic Sensor Net (HCGSN) and recorded with NetStation 4.3.1 software (Electrical Geodesic, Eugene, Oregon). EEG was sampled at 500 Hz, and electrode impedances were kept below 80 KOhm.

Raw EEG data were recorded with the vertex (Cz) as the online reference and re-referenced off-line to an average reference. Stimuli were presented using E-Prime 2.0 software (Psychology Software Tools). The experiment took place in a sound-attenuated, dimly lit room, and the stimuli were presented on a 17-inch computer monitor with a viewing distance of 80 cm.

EEG recordings were processed off-line using NetStation 4.3.1 software (Electrical Geodesics, Inc., Eugene, Oregon). EEG data were bandpass filtered offline at 0.3–40 Hz, and then segmented into epochs containing 100 ms before stimulus onset and 800 ms post-stimulus time. Data were then processed using an artifact detection tool that marked channels bad if the recording was poor for > 20% of the time (amplitude threshold (max – min) >100), if eye-blinks (amplitude threshold (max – min) >100) or eye-movements (amplitude threshold (max – min) >100) occurred. All trials containing either an eye movement, an eye-blink, or more than 10 bad channels, were excluded from further analysis. Following this automatic artifact detection, each trial was examined by-hand by a trained observer in order to remove any remaining trials that contained eye-blink or eye-movement artifacts from further analysis. Bad channels in the data of trials containing fewer than 10 bad electrodes were replaced using a spherical spline interpolation algorithm (Srinivasan et al., 1996). The data were then averaged for each participant, re-referenced to an average reference, and baseline corrected to a 100 ms pre-stimulus interval.

Grand average ERPs were generated from the average ERPs of 16 participants (Study 2) who produced on average 52 viable trials per condition with a minimum of viable 30 trials per condition for each individual participant. An average of 52 (human touch), 53 (human non-touch), 55 (object touch), and 51 (object non-touch) trials per participant, out of 72 trials presented in each condition, were used in the analysis. Electrodes and time windows for data

analysis were chosen on the basis of visual inspection of both individual and grand-averaged ERP data across the scalp, which was initially guided by the hypotheses of the experiment as well as initial piloting of 10 participants (Study 1) whose data are not included in the final analyses due to a slight difference in the experimental design. Clusters of left/right hemisphere electrodes (5 left hemisphere, 5 right hemisphere) over the parietal-central region were selected for the statistical analysis of effects related to somatosensory processing (**Figure 2.4**). Additional clusters of left/right hemisphere electrodes (5 left, 5 right) were selected for the statistical analysis of effects related to visual perceptual processing (**Figure 2.5**).

Mean amplitude, peak amplitude, and latency-to-peak amplitude values during the time window of each ERP component were averaged across relevant electrode montages for each participant for each observation condition (see Results section, below). Repeated measures Analyses of Variance (ANOVAs) with within-subject factors Stimulus Type (Human, Object), Touch (Touch, Non-Touch), and Hemisphere (Left, Right) were performed for both the amplitudes and latencies of the somatosensory and temporal-parietal visual processing components Additionally, we investigated whether the occipital P100, which is involved in lower-level visual sensory-perceptual processing, was influenced by the conditions. For this purpose, an ANOVA with within-subject factors Stimulus Type (Human, Object), Touch (Touch, Non-Touch), and Hemisphere (Left, Right) was carried out at O1 and O2 electrodes. Bonferrroni corrections were employed for all paired-sample comparisons. In particular, in places where only two comparisons are reported in the Results section, the p-values were corrected for the total number of the perfomed paried-sample comparisons.

Results

ERP Components

Study 1 – Electrodes Selection

The pilot study was carried out on 10 participants (7 female), undergraduate students of University of Birmingham, in order to identify main ERP components elicited by the observation of human and non-human touch. Additionally, the purpose of this preliminary study was to establish the electrode locations for the somatosensory and extrastriate visual areas. More specifically, ERPs were computed for the broad distribution of electrodes in the central area (13 electrodes) and the parietal-temporal area (10 electrodes) for this pilot study. After the main ERP components were identified in both areas, the final study (Study 2) was conducted on the same electrode array in the temporal area and on the subset of the 10 electrodes in the central area, which was identical to the present array (**Figure 2.2**) except three electrodes on the central line which were excluded, in order to make it possible to include the factor of Hemisphere in the statistical analysis.

ERP waveforms for the average of 13 electrodes in central area and 10 electrodes in temporo-parietal area are represented in **Figure 2.2** and **Figure 2.3.** The somatosensory components were as follows: an early positive-going component peaking at approximately 170 ms (P170), and a late slow-wave component with a mean amplitude difference between approximately 500 and 700 ms. Additional component peaks were observed at approximately 100 ms (N100), 250 ms (N250), and 300 ms (P300), although the condition effects were not clear. (See **Figure 2.2**). In the temporo-parietal area negative-going component peaking at approximately 170 ms (N170) and positive-going component peaking at about 250 ms (N250) were identified. (See **Figure 2.3**).

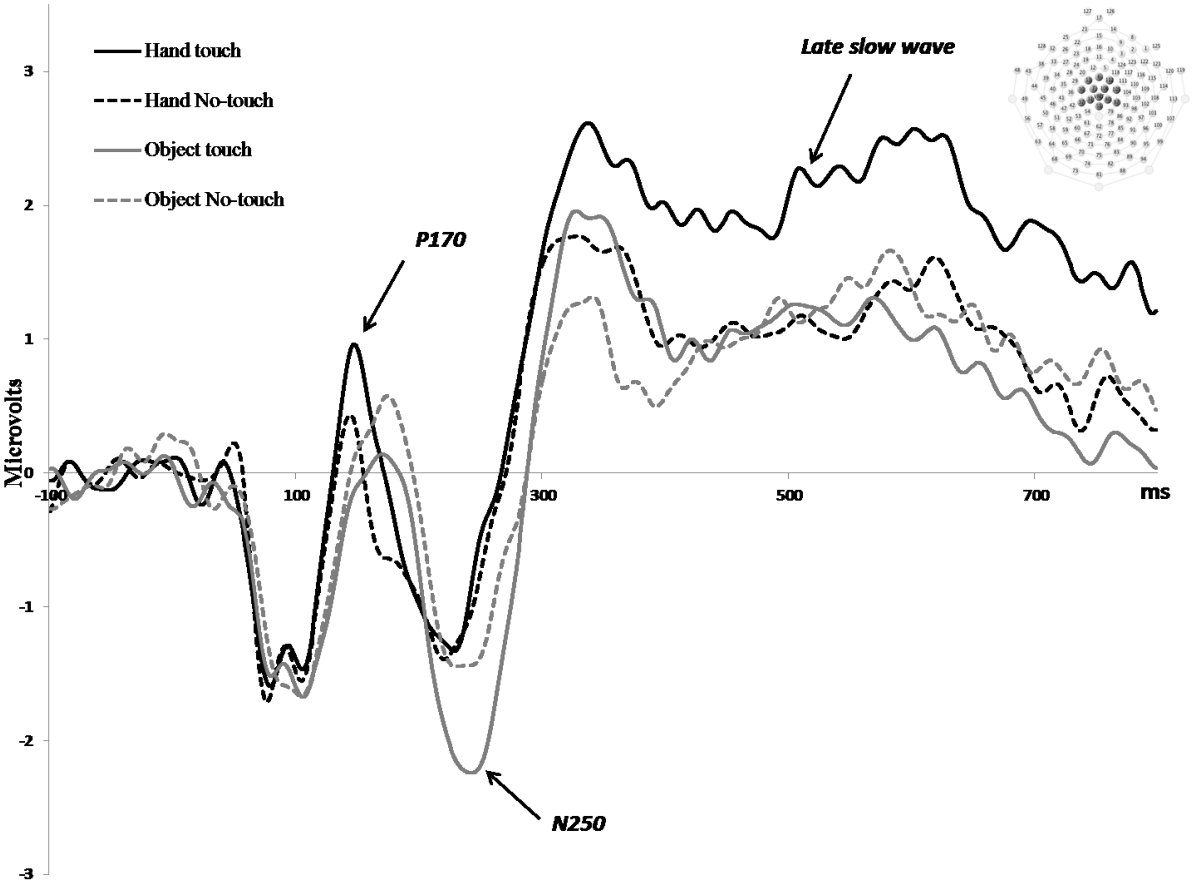

Figure 2.2. **Parietal-Central (Somatosensory) Waveforms –Pilot Study.** The figure represents grand averaged ERP waveforms from 10 participants for the average of electrodes in central area in the four observation conditions and corresponding electrode array. Horizontal line represents ERP latencies (ms) starting from 100 ms before the stimulus onset, vertical line – ERP amplitudes (mV). The arrow points to N170 and N250 components and slow positive waves (500-700 ms) that exhibited latency and amplitude ERP differences between human and object touch and non-touch conditions.

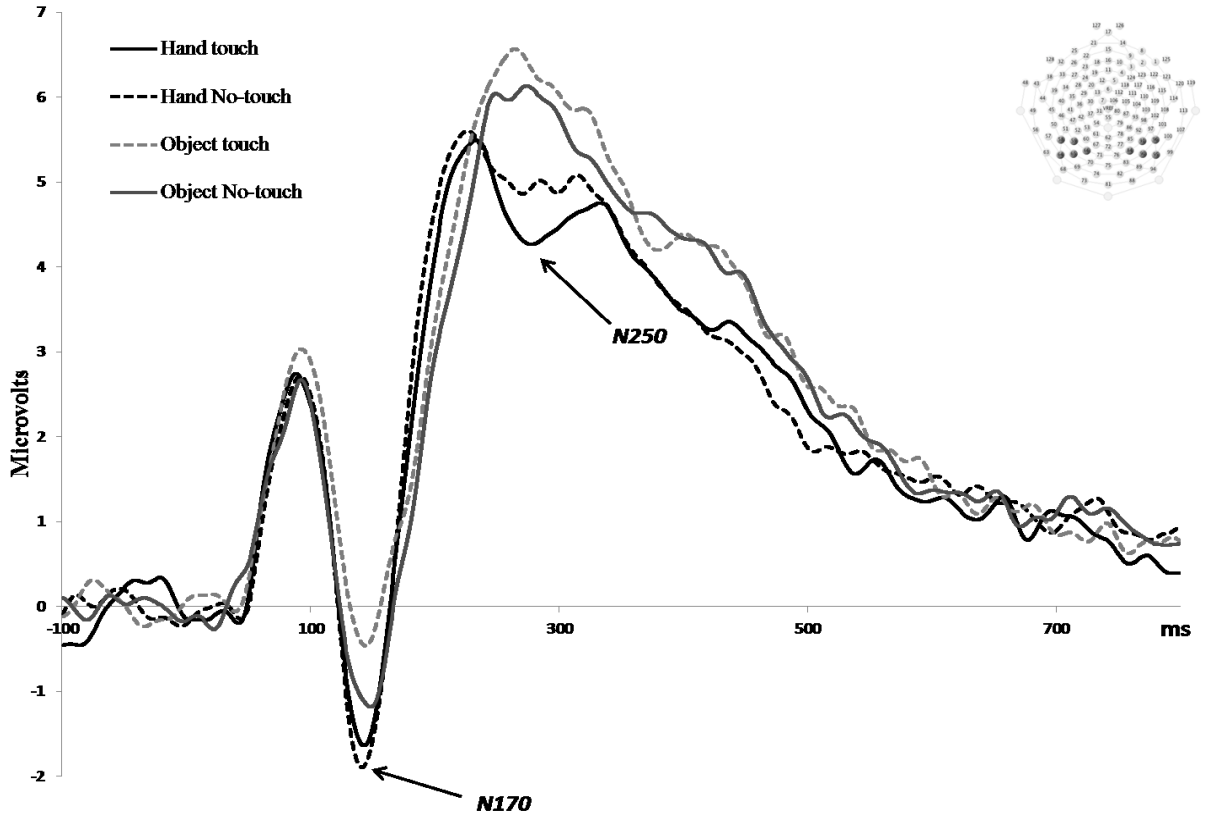

Figure 2.3. **Temporal-Parietal Waveforms – Pilot Study**. The figure represents grand averaged ERP waveforms from 10 participants for the average of 10 electrodes in temporo-parietal area in the four observation conditions and corresponding electrode array. Horizontal line represents ERP latencies (ms) starting from 100 ms before the stimulus onset, vertical line - amplitudes (mV). The arrow points to N170 and N250 components that exhibited amplitude ERP differences between human and non-human conditions.

Final Study –Study 2

Two ERP component effects were identified in parietal-central electrodes over somatosensory cortex. These somatosensory components were as follows, based on their timing in relation to the initial onset of the visual stimulus: an early negative-going component peaking at approximately 100 ms (N100), a positive-going component peaking at approximately 170 ms (P170), and a Late Slow Wave component exhibiting a mean amplitude difference between 500 and 600 ms (**Figure 2.4**). Additional component peaks

were observed at 250 ms (N250) and 300 ms (P300), in these central electrodes, although condition effects were not clearly observed in these components. In addition to these somatosensory components, condition effects were also observed in visual components recorded from electrodes over temporal-parietal cortex (**Figure 2.5**). These were two negative-going peaks that have been shown to be involved in face processing in previous studies, the N170 and N250 components (Bentin et al.1996; Flevaris et al, 2007; Tanaka et al, 2006).

Electrodes used to measure each component were determined through examination of both grand average and individual subject data of pilot participants, and then confirmed as appropriate for the final sample of 16 participants reported here. Ten parietal-central electrodes (5 left hemisphere, 5 right hemisphere) and 10 temporal-parietal electrodes (5 left hemisphere, 5 right hemisphere) were identified for data analysis. Peak amplitudes and latencies to peak amplitudes were analysed for all components except for the Late Slow Wave component, for which mean amplitudes were analysed. Time windows were selected for each component on the basis that the window encompassed the peak of the grand average for each condition, and also accurately measured the peak of the component for each condition for each individual subject. Time windows for data analysis for each component in the parietal-central region were as follows: N100: 70-120 ms, P170: 120-220 ms, N250: 200-270 ms, P300: 240 -340 ms, late positive components: 500-600 ms. For the temporal-parietal components, time windows for analysis were as follows: N170: 120-200 ms, N250: 200-270 ms.

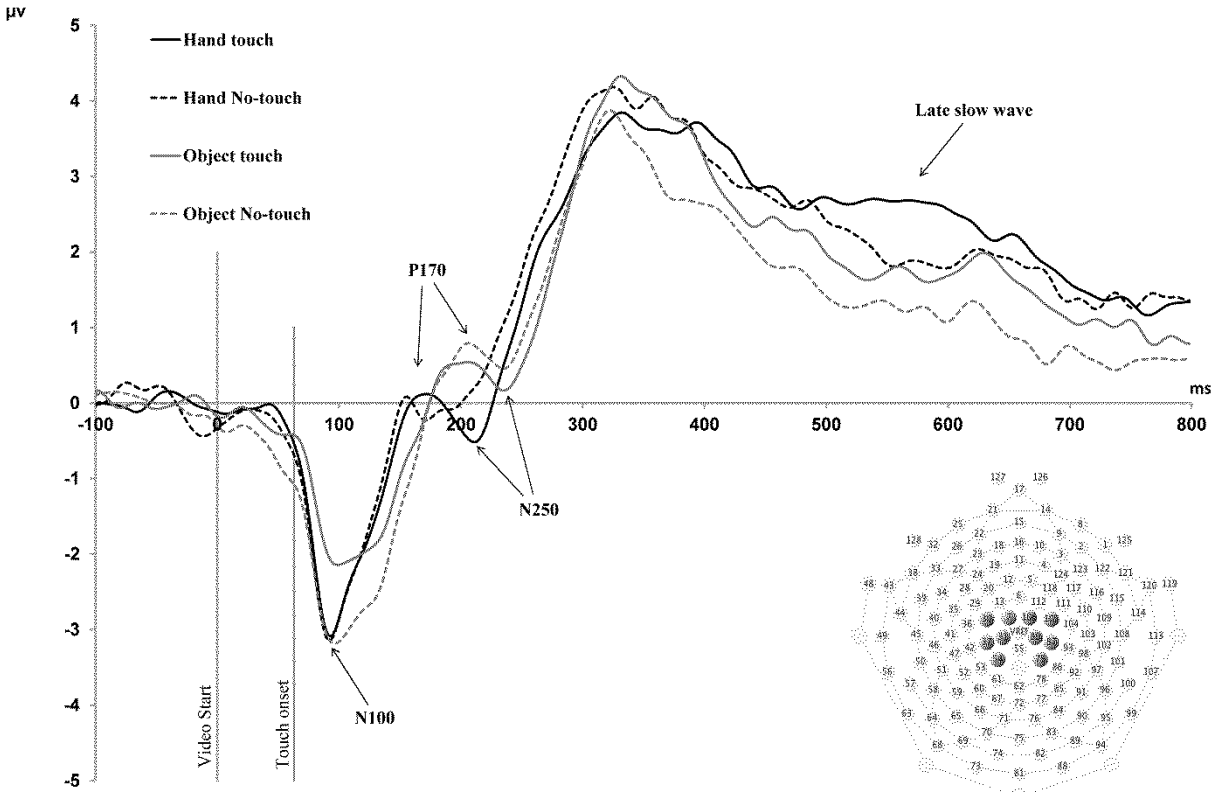

Figure 2.4. Parietal-Central (Somatosensory) Waveforms. Grand average ERP waveforms for parietal-central (somatosensory) electrodes in the four observation conditions. All components are labeled according to their timing in relation to the initial onset of the video stimulus. N100, P170, and N250 component latencies exhibited a main effect of Stimulus Type, whereby latencies for human stimuli were shorter than for objects. The amplitudes of Late Slow Wave component exhibited a main effect of Stimulus Type, whereby amplitudes for human stimuli were larger than for objects. Finally, the peak amplitudes of the N100, N250 and the mean amplitudes of Late Positive Slow Wave (500-600 ms) component exhibited a main effect of Touch, with larger amplitudes for touch compared with non-touch stimuli.

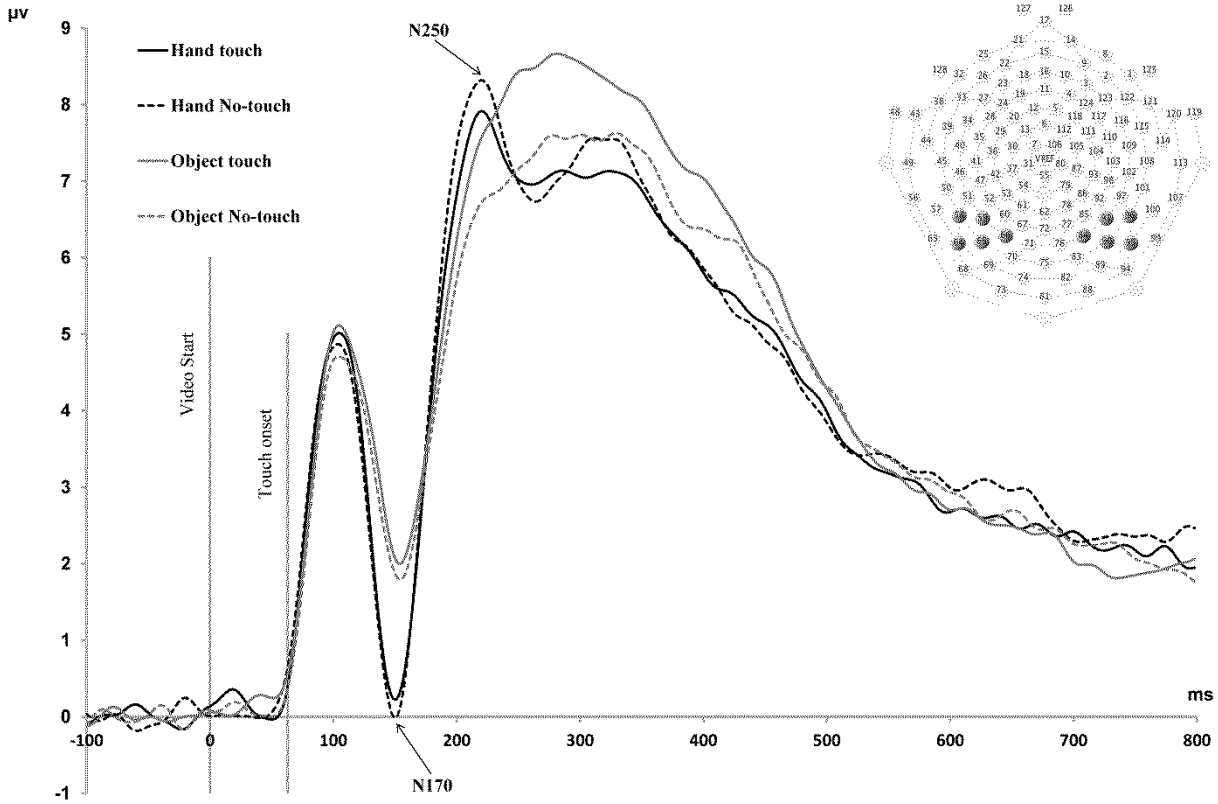

Figure 2.5. Temporal-Parietal Waveforms. Grand average ERP waveforms for temporal-parietal electrodes in the four observation conditions. All components are labeled according to their timing in relation to the initial onset of the video stimulus. The peak amplitudes of the N170 and N250 components exhibited a main effect of Stimulus Type, whereby amplitudes were larger for human stimuli compared to object stimuli. Latencies of the N250 component exhibited a main effect of Stimulus Type, indicating shorter latencies for human versus object stimuli.

Behavioral Responses

The accuracy of the detection of target videos was greater than 90% for all participants.

ERP effects

Parietal-Central (Somatosensory) Components

A repeated measures ANOVA with Stimulus Type (Human, Non-Human), Touch (Touch, Non-Touch), and Hemisphere (Left, Right) as within-subjects factors revealed a main effect of Touch for the peak amplitude of the N100 ($F(1;15)=6.67$, $p<0.05$), N250

components (F(1;15)=5.1, p=<0.05). Additionally, a significant interaction between Touch and Stimulus type was revealed for the amplitude of the N100 component (F(1;15)=9.2, p<0.01). Follow-up paired-sample t-tests revealed a significant difference between non-human touch and non-touch observation (MD=0.6, S.E.=0.2, p<0.05), but not between human touch and non-touch observation (p>0.05). For the N100, the amplitude of object non-touch observation was greater compared with the object touch observation condition (MD=0.4, S.E.=0.2, p<0.05). For both the N250 and late positive components, amplitudes were larger for touch versus non-touch stimuli (**see Figure 2.4**). A main effect of Stimulus Type was observed for the mean amplitudes of the Late Slow Wave Component (F(1;15)=5.18, p<0.05), indicated larger amplitudes for human stimuli compared with objects (see Fig. 2). Finally, a significant interaction between Touch and Hemisphere was revealed for the mean amplitude of the Late Slow Wave Component (500-600 ms; F(1;15)=6.8, p<0.05). Post-hoc paired sample t-tests showed a difference between touch and non-touch conditions in only the right hemisphere (MD=0.58, S.E.=0.2, p=0.01). No other significant main effects of amplitude were observed for N170 and P250 components. No significant effects were observed for the amplitude of P300 component.

A repeated measures ANOVA with Stimulus Type (Human, Non-Human), Touch (Touch, Non-Touch), and Hemisphere (Left, Right) as within-subjects factors revealed a main effect of Stimulus Type for the latencies of the parietal-central N100 component (F(1;15)=7.7, p=0.01), indicating shorter peak latencies for human stimuli (Human=95 ms, S.E.=2.2) than for object stimuli (Object=98 ms, S.E.=2.2; **Figure 2.6**). A main effect of Stimulus Type was also found for the P170 (F(1;15)=15.4, p=0.01; **Figure 2.7)** and N250 (F(1;15)=27.4, p<0. 001; **Figure 2.8**) components, which both also reflected shorter latency responses for human versus object stimuli (P170: Human=183 ms, S.E.=4.5; Object=191 ms,

S.E.=3.4; N250: Human=215 ms, S.E.=3.0; Object=227 ms, S.E.=3.7). Additionally, a main effect of Touch was revealed for the P170 component ($F(1;15)=10.2$, $p<0.01$), with shorter latencies for touch compared to non-touch stimuli (MD=7.8, S.E.=2.5; **Figure 2.7**). No other significant main effects or interactions were observed for the latencies of any of the parietal-central components.

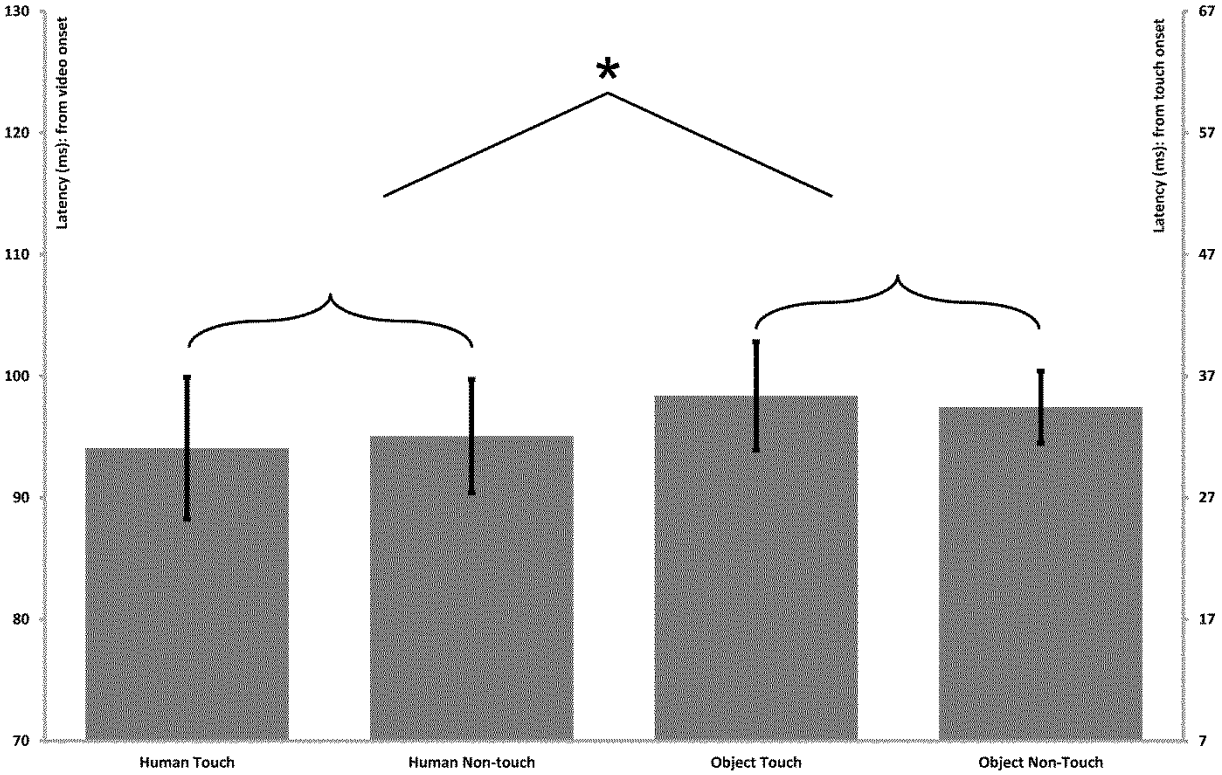

Figure 2.6. Parietal-Central (Somatosensory) N100 Latency Effects. Bar graphs present the mean (standard error) ERP latency differences for the N100 component in the parietal-central region. The left vertical axis presents timing in relation to the initial onset of the video stimulus, and the right vertical axis presents timing in relation to the onset of the touch within the video stimulus. The latencies exhibited a main effect of Stimulus Type, indicating shorter latencies for Human versus Object stimuli.

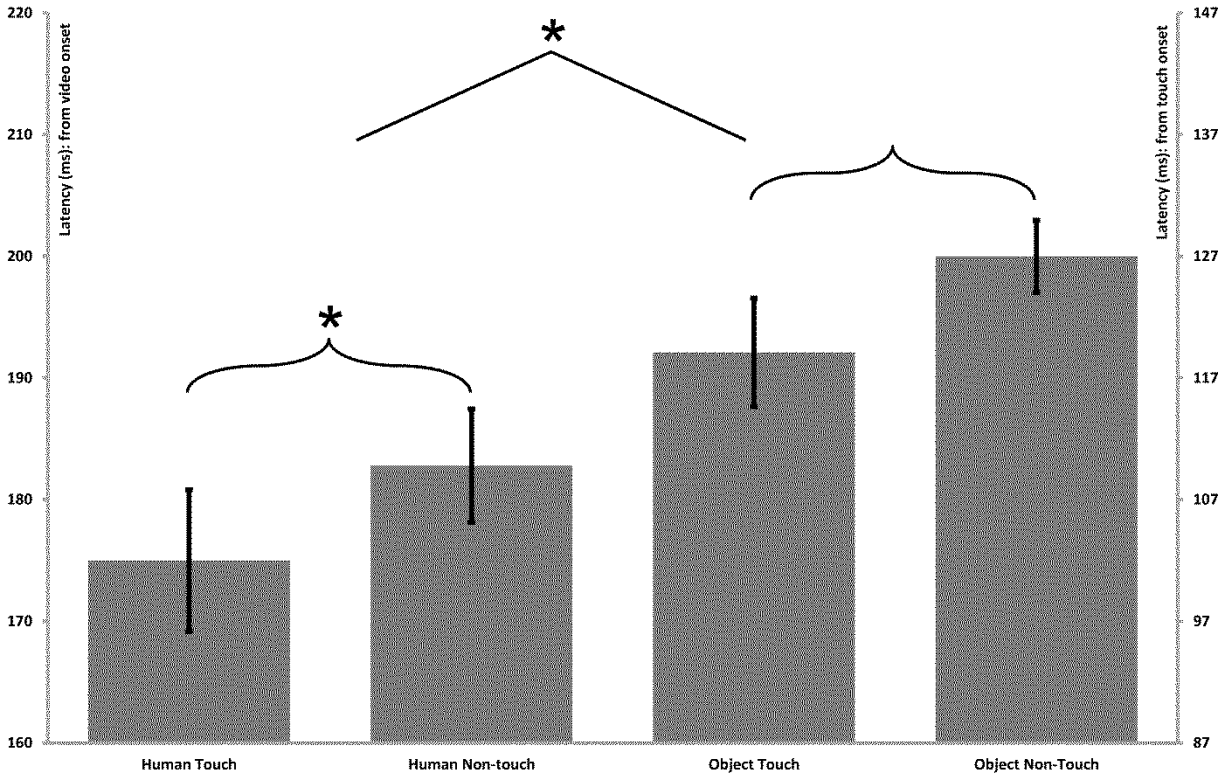

Figure 2.7. Parietal-Central (Somatosensory) P170 Latency Effects. Bar graphs present the mean (standard error) ERP latency differences for the P170 component in the parietal-central region. The left vertical axis presents timing in relation to the initial onset of the video stimulus, and the right vertical axis presents timing in relation to the onset of the touch within the video stimulus. A main effect of Stimulus Type indicated shorter latencies for human versus object stimuli, and a main effect of Touch indicated shorter latencies for touch compared to non-touch stimuli.

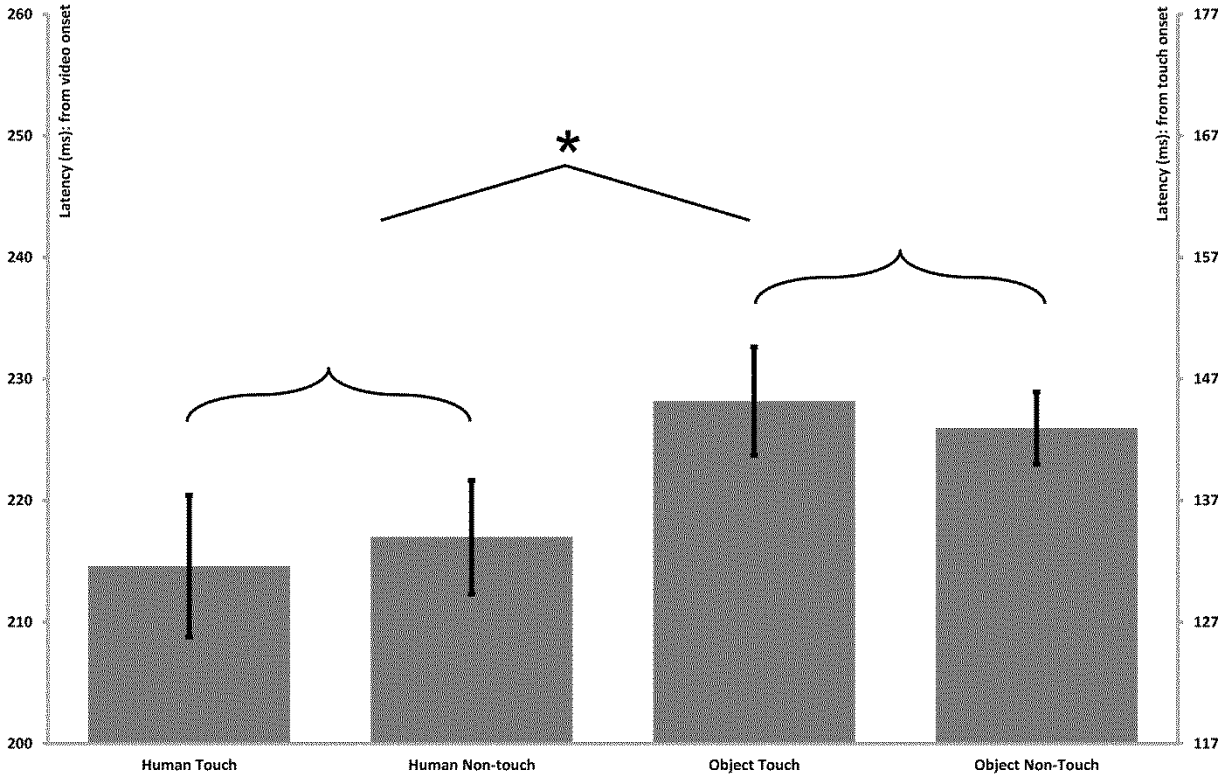

Figure 2.8. Parietal-Central (Somatosensory) N250 Latency Effects. Bar graphs present the mean (standard error) ERP latency differences for the N250 component in the parietal-central somatosensory region. The left vertical axis presents timing in relation to the initial onset of the video stimulus, and the right vertical axis presents timing in relation to the onset of the touch within the video stimulus. The latencies exhibited a main effect of Stimulus Type, indicating shorter latencies for Human versus Object stimuli.

Temporal-parietal (Visual Perceptual) Components

A repeated measures ANOVA with Stimulus Type (Human, Non-Human), Touch (Touch, Non-Touch), and Hemisphere (Left, Right) as within-subjects factors revealed a main effect of Stimulus Type for the peak amplitudes of both the N170 ($F(1;15)=14.9$, $p<0.01$) and N250 components ($F(1;15)=4.7$, $p<0.05$), whereby greater amplitudes were observed for human versus object stimuli. There was also significant interaction between Stimulus Type and Touch for the amplitudes of the N250 component ($F(1;15)=13.7$, $p<0.05$). Post-hoc paired sample t-tests indicated that the peak amplitude was greater for object touch compared to the object non-touch condition (MD=1.2, S.E.=0.4, $p<0.01$). There were no significant

effects of Hemisphere for the amplitudes of either the N170 or N250 components. For latencies, there was a main effect of Stimulus Type for both the N170 ($F(1;15)=4.8$, $p=0.05$) and N250 components ($F(1;15)=17.7$, $p=0.01$), reflecting shorter latencies for human versus object stimuli (Human =148 ms, S.E.= 1.8, Non-human=153 ms, S.E.=2.6; Human=222 ms, S.E.=2.8; Non-human=230 ms, S.E.=3.5). There were no other significant main effects or interactions for latencies of the P100, N170 or N250 components.

Central Occipital (Visual Sensory-Perceptual) Components

A repeated measures ANOVA with Stimulus Type (Human, Non-Human), Touch (Touch, Non-Touch), and Hemisphere (Left, Right) as within-subjects factors was carried out for the latencies or amplitudes of the observed occipital components: the P100, the N150 and the P250 components. No significant effects or interactions observed for either the latencies or amplitudes of the occipital P100 and N150 components, as well as the amplitude of the P250 components ($F(1;15)<1$, $ps>0.1$). A significant main effect of Human was only observed for the latency of the P250 occipital component ($F(1;15)=7.4$, $p<0.05$) which indicated shorter latencies for human compared to non-human stimuli (Human=218 ms S.E.=2.7, Object=224 ms, S.E.=3.5).

Region by Condition Interaction and Correlation Analysis

In order to determine whether modulation in visual areas between the conditions had an impact on the ERP effects found in central areas, correlation analysis of condition by region using Pearson's correlation coefficient was carried out for the amplitudes and latencies of all occipital and central components. No significant correlations between corresponding conditions in different regions were revealed for the latency of the P250 component, and for

the latencies and amplitudes of all other components ($r<0.5$, $p>0.1$, $N=16$). An additional ANOVA was also carried out to determine whether the observed ERP effects (N100, P170, N250) were specific to the central region. Namely, an ANOVA with within-subject factors of Stimulus Type (Human, Object), Touch (Touch, Non-Touch), Hemisphere (Left, Right) and Region (Central, Occipital) was carried out for all components at which either latency or amplitude effects were observed in the central region: N100/P100 (latency and amplitude), P170/N150 (latency), N250/P250 (latency and amplitude). For all components, except the latency of the N250 component, a main effect of Region (All components: $F(1;15)>6$, $p<0.05$) as well as a significant interaction of HumanxRegion (N100, N250, P170: $F(1;15)>3.5$, $p<0.05$), or TouchxRegion (N100: $F(1;15)=4.7$, $p=0.05$) and HumanxTouchxRegion (N100: $F(1;15)=5.2$, $p>0.05$, P170: $F(1;15)=2.5$, $p=0.1$) were observed. The post-hoc paired sample comparisons confirmed that the differences between corresponding conditions expressed by significant main effects and interactions were specific to the central area, while no effects were revealed in the occipital area ($p>0.1$).

Mean amplitude (standard error) and mean latency (standard error) values for all parietal-central, temporal-parietal, and occipital components analysed are presented in **Table 2.1**.

ROI	Central				Temporo-parietal				Occipital			
Conditions	Human Touch	Human Non-touch	Object Touch	Object Non-touch	Human Touch	Human Non-touch	Object Touch	Object Non-touch	Human Touch	Human Non-touch	Object Touch	Object Non-touch
N100 (P100 occipital)	-6.3 (0.59)	5.75 (0.73)	-5.91 (0.48)	-6.85 (0.66)	5.79 (0.47)	5.77 (0.37)	5.87 (0.39)	5.85 (0.42)	8.3 (0.69)	7.9 (0.6)	8.5 (0.64)	8.6 (0.84)
	94 (2.20)	95 (2.50)	98 (2.39)	97 (2.25)	104 (2.29)	102 (2.72)	106 (2.04)	106 (2.46)	105 (2.45)	103 (2.42)	105 (2.29)	105 (2.36)
P170 (N170, N150 occipital)	-2.86 (0.39)	2.74 (0.52)	-2.73 (0.44)	-3.04 (0.45)	0.23 (0.41)	-0.09 (0.43)	1.74 (0.49)	1.43 (0.42)	2.6 (0.7)	2.1 (0.67)	3.1 (0.75)	2.8 (0.7)
	175 (5.83)	183 (4.66)	192 (4.45)	200 (2.97)	150 (2.04)	149 (2.29)	153 (2.69)	153 (2.67)	148 (2.1)	149 (2.05)	150 (3.1)	150 (3.3)
N250 (P200 occipital)	-1.21 (1.06)	-0.19 (1.30)	-0.53 (1.44)	0.02 (1.42)	6.93 (0.62)	7.32 (0.74)	6.84 (0.68)	6.08 (0.7)	11.07 (0.99)	11.6 (1.06)	10.4 (0.99)	10.1 (1.01)
	215 (2.2)	217 (2.5)	229 (2.39)	227 (2.25)	209 (2.77)	207 (3.4)	218 (2.96)	209 (3.62)	217 (3.25)	218 (3.75)	226 (3.7)	221 (4.75)
P300	3.47 (0.6)	3.99 (0.72)	3.41 (0.79)	3.39 (0.66)	-	-	-	-	-	-	-	-
	316 (5.48)	312 (5.08)	318 (4.78)	312 (5.09)	-	-	-	-	-	-	-	-
LSW (500-600 ms): Left Hemisphere	1.28 (0.32)	1.7 (0.43)	2.45 (0.61)	2 (0.51)	-	-	-	-	-	-	-	-
LSW (500-600 ms): Right Hemisphere	1.59 (0.39)	2 (0.50)	2.3 (0.58)	2.19 (0.55)	-	-	-	-	-	-	-	-

Rows in white indicate amplitude (mV), rows in grey indicate latency (ms)

Table 2.1. Mean ERP Component Amplitudes. The table presents the mean amplitudes and their standard errors for each of the components in the parietal-central, temporal-parietal and occipital regions. All components are labeled according to their timing in relation to the initial onset of the video stimulus.

Discussion

In the present study, we investigated the time-course of activation of somatosensory processing mechanisms during the observation of humans versus objects being touched. The results demonstrate that touch processing elicited different levels of somatosensory activity at early sensory, perceptual, and later cognitive stages of processing. The results further demonstrate that somatosensory (parietal-central) and visual perceptual (temporal-parietal) ERP component responses have shorter latencies for stimuli that involve humans versus objects at several stages of processing. Importantly, no differences were observed in the occipital the P100 and the N150 components, and the effects found in the central area (N100, P170, N250) expressed by significant main effects and interactions, except the latency of the N250 component, were specific to the central area only. Although a main effect of Human was also observed for the latencies of the P250 component in the occipital region, no correlations of this particular component, and other component activity for corresponding conditions with the effects in the central area were revealed. This suggests that these differences observed in somatosensory and visual perceptual processing components were not driven by lower-level visual sensory processing differences. On the other hand, the main effect of Human revealed for the latency of the P250 component in the occipital area might be attributed to processing different visual-perceptual characteristics of object stimuli, such as luminance and higher contrast with darker background, when compared to hand stimuli.

The current findings are largely consistent with previous fMRI results that suggest that there is significant overlap in levels of activation of the somatosensory cortex during the observation of human and non-human touch (Ebisch et al., 2008; Keysers et al, 2004). The current results extend this research by providing evidence that the time-course of the

activation of somatosensory processing mechanisms is also similar during human and non-human touch observation. The touch effects in our experiment were observed in larger amplitude responses recorded from electrodes over somatosensory cortex at 100 ms (N100), at 250 ms (N250), and then again between 500 and 600 ms (Late Slow Wave; LSW), for the observation of both human and object touch. These findings suggest that touch observation modulates somatosensory cortex at the early sensory-perceptual (N100), perceptual (N250), and late cognitive (LSW) stages. We note here that the onset of touch within our videos occurred 63 ms after video onset, indicating that the modulation of somatosensory processing occurred at approximately 40 ms (N100), 190 ms (N250), and 440 to 540 ms (LSW), following observed touch.

The finding of modulation of somatosensory cortex 40 ms (N100) after observed touch is consistent with previous evidence for early modulation of somatosensory responses induced by median nerve stimulation at approximately 45 to 55 ms, during the observation of human touch and painful stimulation (Bufalari et al., 2007, Martinez-Jauand et al., 2012). However, it is worth noting its inverse polarity compared to P45 component responses associated with both painful and neutral touch (Bufalari et al., 2007, Peyron et al., 2004). Because the polarity of the evoked potentials is determined by the direction of the current flow, positivity on the surface can be due to soma excitation or to hyperpolarization of the dendrites, while soma inhibition and depolarization of the dendrites can both lead to surface negativity (Humphrey, 1968a, 1968b). Thus, it is impossible to say whether both positive P45 activity during touch and negative N40 (N100) during the observation of touch are caused by excitatory or inhibitory neural activity in the somatosensory cortex. However, the present data suggest that somatosensory activity can be evoked not only by tactile stimulation, but also by

mere observation of touch and this modulation occurs at approximately the same time, as the somatosensory responses induced by touch and pain.

In addition, however, we observed modulation of the late somatosensory cortex response from 440 to 540 ms (LSW) after observed touch. This finding is consistent with a previous MEG study demonstrating that the observation of human touch versus non-touch elicited somatosensory differences between 300 and 600 ms after stimulus onset (Pihko et al., 2010).

Only the N100 recorded from electrodes over somatosensory cortex exhibited an interaction between stimulus type (human, non-human) and touch (touch, non-touch). Specifically, the amplitudes of this negative-going component were less negative in response to the observation of objects not being touched compared with all other conditions. (See **Figure 2.4**). One possible explanation is that the presence of touch in the videos showing non-human objects created associations of the non-animate object (white roll) with a human arm. Alternatively, or additionally, the observation of objects being touched may have generated representations related to intentions associated with a human touching an object with another object, even though no human was visible or apparent. As a result of this, neural responses during the observation of non-human touch might evoke similar mechanisms to human touch and human non-touch at this stage of processing, whereas the observation of non-human non-touch did not.

Although none of the ERP component differences observed for touch versus non-touch processing in the current study were specific to the observation of human touch, the latencies of several ERP components recorded over these same somatosensory regions (Central N100, P170, and N250) were significantly shorter for stimuli presenting human compared with non-human object stimuli. Interestingly, these latency differences between

human and non-human stimuli began at a relatively early sensory-perceptual stage of information processing, approximately 40 ms post-touch observation (N100), and continued through to an early cognitive stage of processing (N250). These results are consistent with other findings that demonstrate the involvement of somatosensory cortex in the processing of social information. For example, Pitcher and colleagues found that repetitive TMS (rTMS) targeted at the face representation region in right somatosensory cortex impaired participants' accuracy in the recognition of facial expressions of emotion, relative to rTMS targeted at either the finger region or the vertex (Pitcher et al, 2008). Interestingly impairment in emotion recognition occurred when the pulses were delivered prior to 170 ms following stimulus onset, which is known to be a critical time for the visual-perceptual encoding of faces in temporal-parietal regions (Righi et al, 2012, Utama et al, 2009). The authors, therefore, suggest that the perceptual encoding of social information that includes somatosensory content is also encoded in somatosensory cortex processing simultaneous with, or prior to, visual perceptual encoding in temporal-parietal regions. Our results are consistent with these previous findings, in that human versus non-human hand encoding difference occurred first at 100 ms (N100) over somatosensory regions and then, later, at 170 ms (N170) over temporal-parietal cortex.

It is worth noting though that there could however be another low-level explanation of human versus non-human effects, specifically the N250 latency effect, in the central area. As mentioned earlier, a significant main effect of Human was revealed for the latencies of P250 component in the occipital region. Although additional correlation analysis did not reveal significant correlations of the N250 central activity for any conditions with the P250 occipital component, the possibility of the visual processing of stimuli having an impact on the ERP effects in the central region cannot be completely ruled out. Despite that the P250 effect in

occipital area can be attributed to differences in visual-perceptual characteristics of stimuli, such as differences in luminance and smoothness of object movement, this finding represents a main limitation for the interpretation of latency effects characterizing processing human versus object stimuli compared in the central area, which should be addressed in the future research.

The current finding of larger amplitude responses to human stimuli in the temporal-parietal N170 and N250 components is consistent with previous studies suggesting differential processing of objects and socially relevant stimuli, including faces and human bodies, in these components (Bindemann et al., 2008; Rossion & Caharel 2011). Specifically, the N170 has been shown to exhibit larger amplitude response for faces than for a variety of non-face objects (Bentin et al., 1996), and recent evidence suggest that face specific response of N170 may reflect specialized mechanisms associated with encoding of face information due to extensive exposure to faces as a social stimulus (Anaki et al., 2007; Flevaris et al., 2007; Macchi-Cassia et al., 2006, Tanaka & Curran, 2001). The N250 component has been found to be larger in amplitude in response to repeated versus non-repeated faces, suggesting a functional link to facial identity and semantic information processing (Tanaka et al, 2006; Pierce et al, 2011).

At both 170 ms (central P170 latencies, temporal-parietal N170 amplitudes) and 250 ms (central N250 amplitudes, temporal-parietal N250 amplitudes), temporal-parietal visual processing effects co-occurred alongside somatosensory component effects in the present study. Previous research suggests that there is integration of processing in somatosensory and extrastriate visual cortex regions for socially relevant touch processing (Serino & Haggard, 2010; Sereno & Huang, 2006). For example, Haggard (2007) found evidence that somatosensory cortex activity is influenced by visual input, such that seeing the body

increased tactile acuity (Haggard, 2007). There is also evidence to suggest the involvement of SI in the visual processing of tactile events (Bolognini et al, 2011). Given this prior evidence, the simultaneous ERP effects at both 170 and 250 ms in central and temporal-parietal regions in the current study may reflect the integration and/or coordination of social and/or touch observation processing in these two regions.

The extent to which neural mechanisms associated with the observation of touch are specific to the observation of human touch is especially intriguing considering that the existing neuroimaging findings have provided somewhat mixed results. In 2008, Ebisch and colleagues demonstrated that the activation of somatosensory cortex during the observation of an object accidentally touched by another object was not different from that in a condition where a human body was touched with an object. The authors therefore suggested that the same mechanisms are involved in the observation of any type of touch. In contrast to this, Blackmore and colleagues reported increased Blood-Oxygen Level Dependent (BOLD) responses in both SI and SII for human touch compared with non-animate touch (Blackmore et al., 2005). Although our ERP results can not provide such detailed examinations of the involvement of particular somatosensory brain regions, our results provide further support for the hypothesis that the observation of both human and non-human object touch elicit neural processing in somatosensory regions (similar to Ebisch et al., 2008; Keysers et al., 2004). Specifically, we observed larger amplitude brain activity during the observation of touch versus non-touch for both human and non-human stimuli in both the N250 component and a late slow wave component (500 – 600 ms) recorded from electrodes over somatosensory cortex. Additionally, for the latter component, an interaction between Touch and Hemisphere was revealed, indicating that the touch versus non-touch effect was greater in the right than in the left hemisphere. We note that this finding of lateralization of processing cannot be

attributed to the experimental design features or participant sample, because the presentation of right and left hands was counterbalanced within the experiment, and only right handed participants were included in the study. There, we suggest that this effect might reflect an increase of late cognitive processing or evaluation of observed touch stimuli in the right hemisphere.

It is worth considering why the neural mechanisms recruited during the observation of touch did not differ for human versus non-human touch in the current ERP study or in Ebisch and colleagues' fMRI study (Ebisch et al., 2008; see also Keysers et al., 2004). As suggested above, it is possible that the presence of intention during touch may make the observed touching of both human and non-human stimuli more animate compared with non-touch. Similarly, it has been argued that the recruitment of neural mechanisms for the observation of human touch may carry over to the observation of non-human object touch. This type of effect may be more likely in studies, including the current study, in which participants are primed to the potential self/other nature of the stimulus set through being touched with the touching objects utilised in the experiment (see e.g., Ebisch et al., 2008, for discussion). Although this interpretation reflects a potential limitation for our full understanding of the implications of the current results as well as the results of several previously published fMRI studies on this topic, we note that this particular interpretation would suggest a surprising predominance and flexibility of social mechanisms for somatosensory processing. This, in itself, is an unlikely but intriguing possibility, which is certainly worth pursuing in future research.

In summary, the current findings reflect the first examination of the time-course of the neural mechanisms involved in the observation of human versus object touch. The study results provide new evidence, consistent with existing fMRI evidence, to suggest that

somatosensory processing mechanisms are recruited during the observation of both human and object touch. The current results further indicate that the time-course of these touch observation mechanisms does not differ for human versus object touch, both of which occur at several stages of processing. In addition, we found new evidence for the hypothesis that the somatosensory processing system responds more quickly to the presentation of human versus object stimuli, which was reflected in both early sensory-perceptual and perceptual processing ERP component effects recorded from electrodes over somatosensory cortex. These somatosensory processing mechanisms both precede and follow the expected perceptual encoding of human versus non-human objects in extrastriate visual cortical regions.

CHAPTER 3:

NEURAL MECHANISMS OF THE OBSERVATION OF HAND AND OBJECT TOUCH IN CHILDREN

The following chapter has been submitted as a publication to the British Journal of Developmental Psychology as a special issue on action mirroring and is authored by Alena Galilee and Joseph McCleery. The format of the manuscript has been altered in a few places and small changes to the text have been made to make it consistent with other chapters.

Abstract

Previous neuroimaging research has shown that somatosensory mechanisms are activated when adults observe another person or object being touched. In Chapter 2, it was shown that somatosensory activations during touch observation are apparent at both an early cognitive stage (before 300 ms) and a late cognitive stage (500 – 600 ms) in event-related potential (ERP) activity recorded over somatosensory cortex. In this study, we measured ERPs from 4- to 5-year old children to investigate the development of the neural mechanisms involved in the observation of human and object touch. Participants were presented with video clips of an arm or a cylindrical object being touched. As in a previous study of adults, touch versus non-touch effects were observed in the amplitudes of the LSW component (600 – 700 ms) measured from electrodes over somatosensory cortex. Additionally, human versus non-human stimulus effects were reflected in the amplitudes of the N100 component recorded over somatosensory cortex, as well as in the latencies of the N170 component recorded over occipital-temporal cortex in children, as in adults. These findings provide evidence that tactile mirroring mechanisms are activated during the observation of touch in children, and further suggest that touch observation mechanisms are relatively mature by 4- to 5-years of age.

Introduction

The neural mechanisms underlying social-cognitive functioning and development have critical relevance to our understanding of both typical and atypical social, emotional, communicative, and cognitive development. One of the most popularly investigated aspects of social-cognitive functioning is the development of neural mechanisms for face-processing. Following decades of highly consistent evidence that extrastriate visual mechanisms involved in the perceptual encoding of faces exhibit both larger amplitude and shorter latency responses to faces than to objects in adults (Bentin et al., 1996, Flevaris at al, 2008, see also Rossion & Gauthier, 2002), recent research has determined that similar patterns of activity are observable in children as young as 4- to 5-years of age (Kuefner et al., 2010). Despite extensive research on the neurodevelopmental basis of face processing, relatively little is known about neural mechanisms for other aspects of social-cognitive development. However, a reasonable amount of previous EEG and fMRI research has focused on two other aspects of social development: somatosensory perception (Rigato et al., 2014, Pihko et al., 2009, Björnsdotter et al., 2014, see more Chapter 4, introduction section) and "mirror neuron" functioning (Oberman et al., 2013; Marshall & Meltzoff, 2014; Vanderwert, Fox & Ferrari, 2013).

Somatosensory perception plays a central role in early social-cognitive development. It was shown that tactile perception is crucial for the development of both fine and gross motor skills in infancy (Corbetta and Snap-Childs, 2009) and pre-schoolers (Case-Smith 1995). Apart from being crucial for the motor development, somatosensation plays an important role in the development of social communication skills in infancy and later childhood (Moszkowsky et al., 2009). Several studies suggest that coordination of visual and

tactile modalities is present in early childhood (Gottfried et al., 1977, see also Picad, 2007). However, although 4 year old children have already an internal body reference, they still make errors in localization of tactile stimuli depending on limb position when visual information is not available (Begum et al., 2014), and the number of localization errors becomes exponentially smaller over age, reaching the adult level by adolescence (Yoshioka et al., 2013). Cross-modal touch-to-vision transfer abilities, such as recognition of objects, which were previously visually presented, by touch was also found to increase between 5- and 8- years of age (Picad, 2007).

In addition to behavioural research, somatosensory evoked potentials in response to tactile stimulation, when accompanied and not accompanied by vision, have been reported in several MEG studies in infants and young children (Gondo et al., 2001, Rigato et al., 2014, Xiang et al., 2004, Gaetz et al., 2008, Pihko et al., 2009, Remijn et al., 2014). Specifically, Rigato and colleagues recorded SEPs in 6.5 to 10 month old infants, in order to examine whether the somatosensory processing is influenced by an uncrossed and crossed arm postures (Rigato et al., 2014). The results showed that an arm posture influenced the mid-latency and early latency SEPs at 8 months and 10 months of age, respectively, suggesting the development of an ability to determine the position of the perceived touch depending on the limb position in the first year of life (Rigato et al., 2014). Additionally, Pihko and colleagues examined SEPs in reponse to tactile stimulation of index finger of children from 1.6. to 6 years of age that showed an early modulation in the somatosensory waveform around 50 ms (M50) over contralateral somatosensory cortex (Pihko et al., 2009). The same study showed that an earlier component at around 30 ms (M30) occurred in toddlers and adults, but not preschool children. Together, results from SEP studies suggest significant maturation changes

in somatosensory processing in infancy and early childhood (see more on the development of tactile perception, Chapter 4, introduction section).

One newly emerging aspect of our understanding of social-cognitive functioning is tactile mirroring. Previous functional magnetic resonance imaging (fMRI) studies of adult participants have demonstrated that the observation of another person being touched can activate somatosensory responses, in core brain regions associated with sensation processing (Ebisch et al., 2008, Schaefer et al., 2006, Schaefer et al., 2009, Keysers et al., 2004). These findings have been interpreted as evidence to suggest that somatosensory activity during the observation of touch may reflect tactile mirroring mechanisms, whereby the observation of an action automatically activates portions of corresponding neural circuitry in the observer (see e.g., Rizzolatti, Craghiero, 2004; Cattaneo & Rizzolatti, 2010).

Most relevant to the current study, we recently utilized event-related potentials to examine the time-course of the activation of somatosensory processing mechanisms during the observation of videos of humans versus objects being touched (Chapter 2: Streltsova & McCleery, 2014). The results of Chapter 2 revealed that the effect of touch was reflected in ERP amplitude differences between touch and non-touch conditions in both early sensory-perceptual components (N100, N250) and late cognitive components (500-600 ms), each measured at the electrodes over somatosensory cortex. Additionally, we observed human versus non-human effects that reflected in ERP differences of early sensory-perceptual components (N100, P170, N250) at electrodes sites over somatosensory cortex as well as visual perceptual components (N170, N250) recorded over the occipito-temporal area and previously associated with social information processing (Chapter 2: Streltsova & McCleery, 2014).

Despite growing interest in this topic, tactile mirroring has only just begun to be

explored in children. One MEG study found that the observation of tactile finger stimulation modulated somatosensory evoked field (SEP) produced by finger touch in 3- to 4-year old children (Remijn et al., 2014). The results of this study also uncovered somatotopic organization of the electromagnetic response during visual-tactile processing, which further suggests the maturation of tactile mirroring at early age. In particular, the strength of equivalent current dipoles (ECDs) was higher when felt and observed touch occurred to the same body part, as opposed to different body parts. Additionally, Remijn and colleagues assessed the time-course of the induced visual-tactile response by examining the latencies of the ECDs over somatosensory cortex. However, due to the stimulus presentation methods utilised in this particular study, including the presence of tactile stimulation in all experimental conditions, the time-course of the observation of touch has not been examined in children thus far. Furthermore, although previous research in adults strongly suggests that the observation of objects being touched can also induce somatosensory responses (Streltsova & McCleery, 2014, Keysers et al., 2004, Ebisch et al., 2008), to date no studies have examined or compared neural mechanisms elicited by the observation of human versus non-human touch in children.

In the current study, we employ an established event-related potentials paradigm in order to examine the nature and time-course of the neural mechanisms associated with human and non-human touch observation in 4- to 5-year old children. The aim of this study is to determine whether or not somatosensory processing mechanisms are automatically activated during the passive observation of human and non-human touch in children and, if so, whether or not the nature and time-course of these mechanisms is similar to those observed previously in adult participants using the same, time-sensitive paradigm.

Based upon previous EEG research that suggests early development of mirror functioning, and also based upon the results of our previous adult study using the same touch observation paradigm (Chapter 2: Streltsova &McCleery, 2014), we hypothesize that somatosensory mechanisms will be activated during the observation of touch. Furthermore, we predict that the relative timing of somatosensory activity reflected in ERP components will be similar to that of mechanisms previously observed in adults (see also Nelson & McCleery, 2008). Specifically, we hypothesize that touch versus non-touch effects will occur at both an early stage of processing (e.g., N100) and a late stage of processing (Late Slow Wave) in electrodes located over somatosensory cortex. We further hypothesize that specialist somatosensory activity will occur in response to Human versus Non-Human stimuli, at an early stage of processing reflected in the waveforms of N100 component (over the parietal-central region). Finally, we predict that Human versus Non-Human activity differences will occur over occipital-temporal regions (e.g., occipital-temporal N170 component) in children, as in adults (Chapter 2: Streltsova & McCleery, 2014).

Methods

Participants

Participants were 40 (21 female, 19 male) 4- and 5-year-old children from the city of Birmingham and surrounding districts, in the West Midlands region of the United Kingdom. These participants had a mean age of 55 months (range: 50-69 months) (see **Table 3.1**, for participants' characteristics). The parents of thirty six participants included in the study reported that their child was right-handed, and four participants were reported as being left-handed. Data from six additional participants were excluded from analysis because they

produced fewer than 30 trials of viable EEG/ERP data in one or more of the four experimental conditions. Parents of all participants reported that their child had no history of a neurological or psychiatric disorder, and that they had normal or corrected to normal vision. Informed written consent was obtained from parents of all participants prior to participation in the study, in accordance with an ethical protocol approved by the Ethical Review Committee of the University of Birmingham.

Materials

Materials were identical to those used in a previously published study of adult participants (Chapter 2: Streltsova & McCleery, 2014). Videos were in .avi format and were recorded using a digital camera with a resolution of 720 x 480 color pixels, and with a frame rate of 29.97 frames/second, positioned 60 cm from the actor or object. The following parameters were used for all of the video recordings: frequency rate: 29.97 Hz, 75 frames, pixel aspect ratio: 1.067. All video clips were created using Pinnacle Studio 12, and edited down to a length of 25 frames, corresponding to a total duration of approximately 830 ms. All human stimulus video clips presented the right or left palm and forearm of a male or female actor, from an egocentric point of view. All non-human stimulus video clips presented a cylindrical object from either a right or left side orientation. The stimulus set for each condition was comprised of 12 different video clips, 6 videos for each actor or object, for a total of 48 stimuli (see example stimuli in **Figure 3.1**). Each video in the touch condition demonstrated either the left or right palm and forearm of an actor, or an object, and one of three objects (peacock feather, brush, plastic arm massager) approaching the arm or object and subsequently touching it. For the non-touch condition, the videos involved the same

object (feather, brush, plastic arm massager), approaching the arm of the person or object and moving in front of it, but without touching it. Physical characteristics of touch and non-touch conditions, such as the velocity and trajectory of the hand motion, were matched as close as possible. In particular, the final stimuli were selected from a greater pool of videos on the basis of clarity of touch and non-touch and a similar approaching motion and position of touch for all three objects. The average onset of movement in front of an object or touch of an object or person was measured to be precisely 63 ms after the visual onset of the video for each condition. Four additional videos showed pictures of cartoon characters, such as Mickey Mouse and Winnie-the-Pooh. These pictures were used as 'target' trials and were not included in the data analysis. A miniature digital closed-circuit video camera located below the stimulus presentation monitor was used in vivo by an experimenter to identify and mark any trial during which the child was not attending to the visual stimuli, which were then removed from analysis.

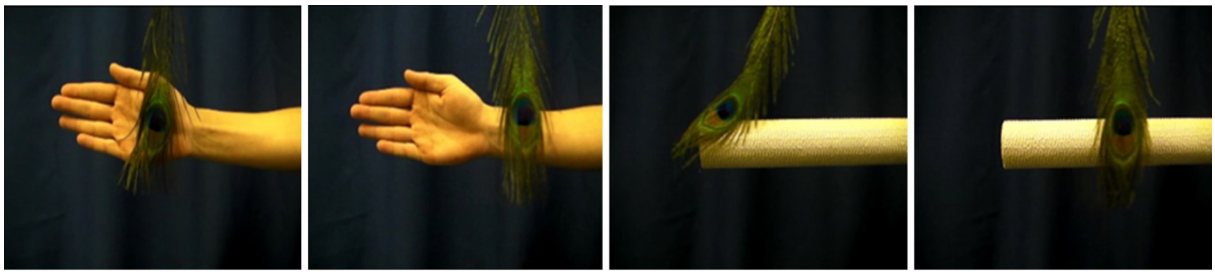

Figure 3.1. Stimuli. Example frames extracted from the video clips in the four experimental conditions: (1) Hand touch (an object moving in front of a male arm and palm and touching it); (2) Hand non-touch (an object moving in front of an arm and palm without touching it); (3) Object touch (an object moving in front of a white roll and touching it); and (4) Object non-touch (an object moving in front of a white roll without touching it).

Experimental procedure

Participants were studied in a between-subjects experimental design, during which they were randomly assigned to observe either Human (Touch, Non-Touch) or Non-Human (Touch, Non-Touch) stimuli. If assigned to the observation of HUMAN touch condition, participants were presented with videos showing an arm with an object touching (touch) it or moving in front of it (non-touch). Alternatively, if assigned to the observation of OBJECT touch condition, participants were presented with videos showing a cylindrical object with another object either touching it or moving in front of it. Participants were required to press a button when they saw a picture of a cartoon character.

Participants were seated comfortably in an isolated sound-attenuated EEG/ERP testing room in front of the computer stimulus monitor. Each ERP observation trial began with a baseline period of 1000 ms, presenting a blank black screen. This was then followed by a central fixation cross, which varied in duration from 800 ms to 1000 ms. Finally, the touch or non-touch video stimulus was presented for 830 ms (25 frames). The order of the trials presented within each block was randomized.

EEG recording and data analysis

EEG data were acquired using a 128-channel Hydrocel Geodesic Sensor Net (HCGSN) and recorded with NetStation 4.3.1 software (Electrical Geodesic, Eugene, Oregon). EEG was sampled at 500 Hz, and electrode impedances were kept below 100 KOhm. Raw EEG data were recorded with the vertex (Cz) as the online reference and re-referenced off-line to an average reference. Stimuli were presented using E-Prime 2.0

software (Psychology Software Tools). The experiment took place in a sound-attenuated, dimly lit room, and the stimuli were presented on a 17-inch computer monitor with a viewing distance of 80 cm.

EEG recordings were processed off-line using NetStation 4.3.1 software (Electrical Geodesics, Inc., Eugene, Oregon). EEG data were bandpass filtered offline at 0.1–40 Hz, and then segmented into epochs containing 100 ms before the video onset and 800 ms post-stimulus time. Data were then processed using an artifact detection tool that marked channels bad if the recording was poor for > 20% of the time (amplitude threshold (max – min) >100). Additionally, trials containing more than 10 bad channels were excluded from further analysis. Following this automatic artifact detection, each trial was examined by hand by a trained observer in order to remove any remaining trials that contained motor, eye-blink, or eye-movement artifacts from further analysis. Bad channels in the data of trials containing fewer than 10 bad electrodes were replaced using a spherical spline interpolation algorithm (Srinivasan et al., 1996). The data were then averaged for each participant, re-referenced to an average reference, and baseline corrected to a 100 ms pre-stimulus interval.

Grand average ERPs were generated from the average ERPs of 20 Human condition and 20 Non-Human condition participants who produced an average of 60 viable trials per condition with a minimum of viable 30 trials per condition for each individual participant. An average of 60 (human touch), 59 (human non-touch), 59 (object touch), and 60 (object non-touch) trials per participant, out of 110 trials presented in each condition, were used in the analysis. Electrodes and time windows for data analysis in the central area were chosen on the basis of visual inspection of both individual and grand-averaged ERP data across the scalp, which was initially guided by the hypotheses of the experiment as well as our previous study of adult participants using the same ERP paradigm (Chapter 2: Streltsova & McCleery, 2014).

Clusters of left/right hemisphere electrodes (5 left hemisphere, 5 right hemisphere) over the parietal-central region were selected for the statistical analysis of effects related to somatosensory processing (**Figure 3.2**). Additional clusters of left/right hemisphere electrodes (4 left hemisphere, 4 right hemisphere) were selected for the statistical analysis of effects related to visual perceptual processing in the occipital-temporal region (**Figure 3.3**). Similarly, visual inspection of electrodes in this region was guided by the initial hypothesis and prediction from the previous study of adults and children of the presence of human versus non-human effects in extrastriate visual areas (Flevaris et al., 2007, Kuefner et al., 2010). As a first step of the electrode selection procedure, the presence of the N170 effects was identified in the ERP waveforms in children, which are commonly considered to be related to social processing of visual stimuli (Rossion and Caharel, 2011). Additionally, previous ERP study of the development of face processing identified a occipito-temporal location of N170 and N250 effects in 4- to 5- year old children compared to a broader temporal-parietal distribution in older children and adults (Kuefner et al., 2010, Taylor et al., 2004). Following this hypothesis driven identification of N170 effects in children, the location of the electrodes in occipito-temporal regions was further confirmed by visual inspection of individual subject and grand average data.

Mean amplitude for the Late Slow Wave (LSW) component and peak amplitude and latency-to-peak values for all other ERP components were averaged for the relevant time windows, across the relevant electrode montages for each participant for each observation condition (see below Results). Repeated measures Analyses of Variance (ANOVA) with within-subjects factors of Touch (Touch, Non-Touch) and Hemisphere (Left, Right) and a between-subjects factor of Stimulus Type (Human, Object) were performed for both the amplitudes and latencies of the somatosensory and occipital-temporal visual processing

components. Additionally, we investigated whether the occipital components P100 and P300, involved in lower-level visual sensory-perceptual processing, were influenced by the conditions. Specifically, an ANOVA with within-subjects factors Touch (Touch, Non-Touch) and Hemisphere (Left, Right) and a between-subjects factor of Stimulus Type (Human vs Object) was carried out for the components P100, N200 and P300 at the cluster of electrodes (4 left hemisphere, 4 right hemisphere) in the occipital area. Paired-sample t-tests were performed to further explore significant main effects and interactions. Bonferroni corrections were employed for all post-hoc paired sample comparisons.

Results

ERP Components

The somatosensory components were as follows, based on their timing in relation to the initial onset of the visual stimulus: an early negative-going component peaking at approximately 100 ms (N100), a positive-going component peaking at approximately 170 ms (P170), a negative-going component peaking at approximately 350 ms (P400), and a Late Slow Wave component exhibiting a mean amplitude difference between 600 and 700 ms (**Figure 3.2**). Between-group (Human, Object) effects were also observed in the ERP components recorded from electrodes over occipital-temporal cortex (**Figure 3.3**).

Electrodes used to measure each component were determined based on the results of Chapter 2 (Streltsova & McCleery, 2014) and visual inspection of both grand average and individual data of 40 participants reported in the current experiment. Ten parietal-central electrodes (5 left hemisphere, 5 right hemisphere) and 8 occipital-temporal (4 left

hemisphere, 4 right hemisphere) electrodes were identified for the analysis (see Methods). Peak amplitudes and latencies to peak amplitudes were analysed for all components except for the Late Slow Wave component, for which mean amplitudes were analysed. Time windows were selected for each component on the basis that the window encompassed the peak of the grand average for each condition, and also accurately measured the peak of the component for each condition for each individual subject. Time windows for data analysis for each component in the parietal-central region were as follows: N100: 70-150 ms, P170: 120-200 ms, P400: 330-430 ms, LSW components: 600-700 ms. For the occipital-temporal components, time windows for analysis were as follows: P100: 70-150 ms, N170: 130-230 ms.

Characteristics	TD children assigned to Human group (n=20)	TD children assigned to Object group (n=20)	Group comparison (p value)
Handedness	18 right, 2 left	18 right, 2 left	N/A
Gender	10 male, 10 female	9 male, 11 female	N/A
Chronological age in months (SD)	55 (8.8)	55 (10)	p=0.75

Table 3.1. Participants' characteristics. Characteristics of children who observed object and human stimuli and the results of the group comparisons based on independent sample t-tests.

ERP effects

Parietal-Central (Somatosensory) Components

A repeated measures ANOVA with Touch (Touch, Non-Touch) and Hemisphere (Left, Right) as within-subjects factors and Stimulus Type (Human vs Object) as between-subjects factor revealed a main effect of Touch for the Late Slow Wave component (600-700 ms) ($F(1;38)=7.3$, $p=0.01$), indicating larger amplitude for touch compared with non-touch

stimuli (Touch= -2.1 mV, Non-touch= -0.9 mV, S.E.=0.5) (see **Figure 3.2**). Additionally, a significant interaction between Hemisphere and Stimulus Type was revealed ($F(1;38)=10.7$, $p<0.01$). Post-hoc paired sample t-tests showed increased processing in the left compared to the right hemisphere in the group of children who observed objects (Left= -2.5 mV, Right =0.4 mV, S.E.=0.7, $p<0.05$), but not in the children who observed human stimuli ($p>0.1$). No other effects or interactions were observed for the Late Slow Wave component ($F(1;38) <2.1$, $p>0.1$).

A repeated measures ANOVA with Touch (Touch, Non-Touch) and Hemisphere (Left, Right) as within-subjects factors and Stimulus Type (Human vs Object) as a between-subjects factor revealed a significant effect of Stimulus Type for the amplitude of the parietal-central N100 component ($F(1;38)=4.1$, $p<0.05$), indicating greater amplitudes for human stimuli compared to objects (Human= -5.7 mV, Object= -4 mV, S.E.=0.6) (see **Figure 3.2**). No other significant main effects or interactions were observed for the amplitude and latencies of any of the parietal-central components ($F(1;38) <1.1$, $p>0.1$).

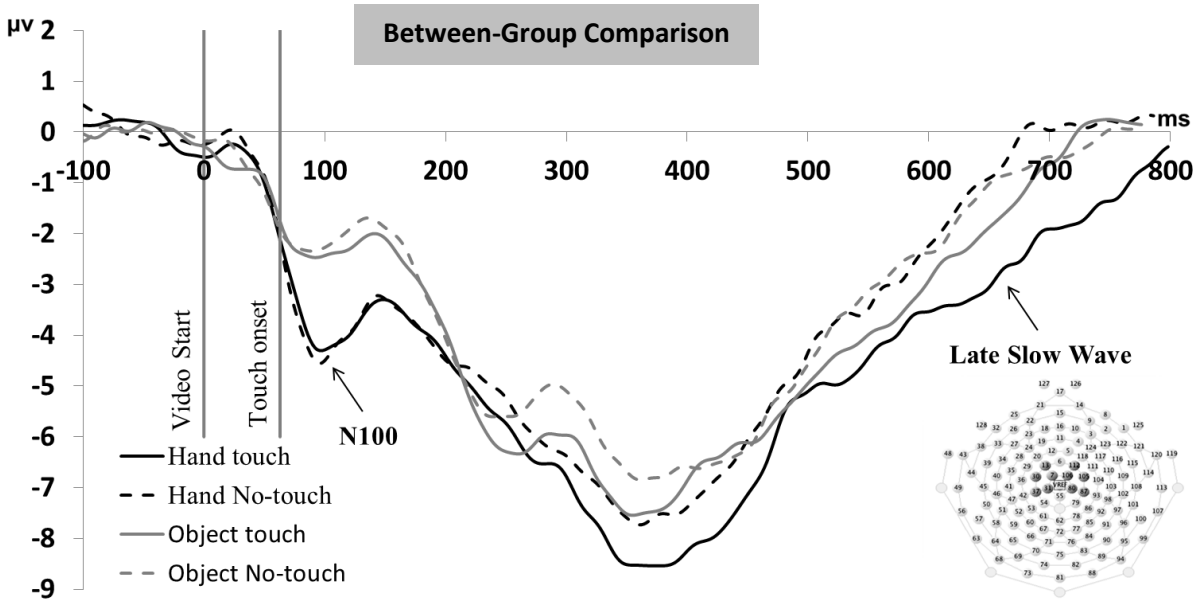

Figure 3.2. Parietal-Central (Somatosensory) Waveforms. Grand average ERP waveforms for parietal-central (somatosensory) electrodes in the touch and non-touch conditions in two groups of children who observed human stimuli and objects. All components are labelled according to their timing in relation to the initial onset of the video stimulus. The amplitude of N100 component exhibited a main effect of Stimulus Type, whereby the amplitude for human stimuli was larger when for objects. The amplitudes of the Late Slow Wave component (600-700 ms) exhibited a main effect of Touch, with larger amplitude to touch compared to non-touch stimuli.

Occipital-Temporal (Visual Perceptual) Components

A repeated measures ANOVA with Touch (Touch, Non-Touch) and Hemisphere (Left, Right) as within-subjects factors and Stimulus Type as a between-subjects factor revealed a significant effect of Stimulus Type for the latencies of N170 component in the occipital-temporal area ($F(1;38)=7.5$, $p<0.01$). Post-hoc paired sample t-tests showed that the latencies of the N170 component were shorter for human stimuli compared to objects (Human=166 ms, Object=192 ms, S.E=6.7, $p<0.01$) (see **Figure 3.4**). There were no significant effects observed for the amplitude of N170 component ($F(1;38) =1.2$, $p>0.1$) as well as the latency and amplitude of the P100 component ($F(1;38)=0.2$, $p>0.1$).

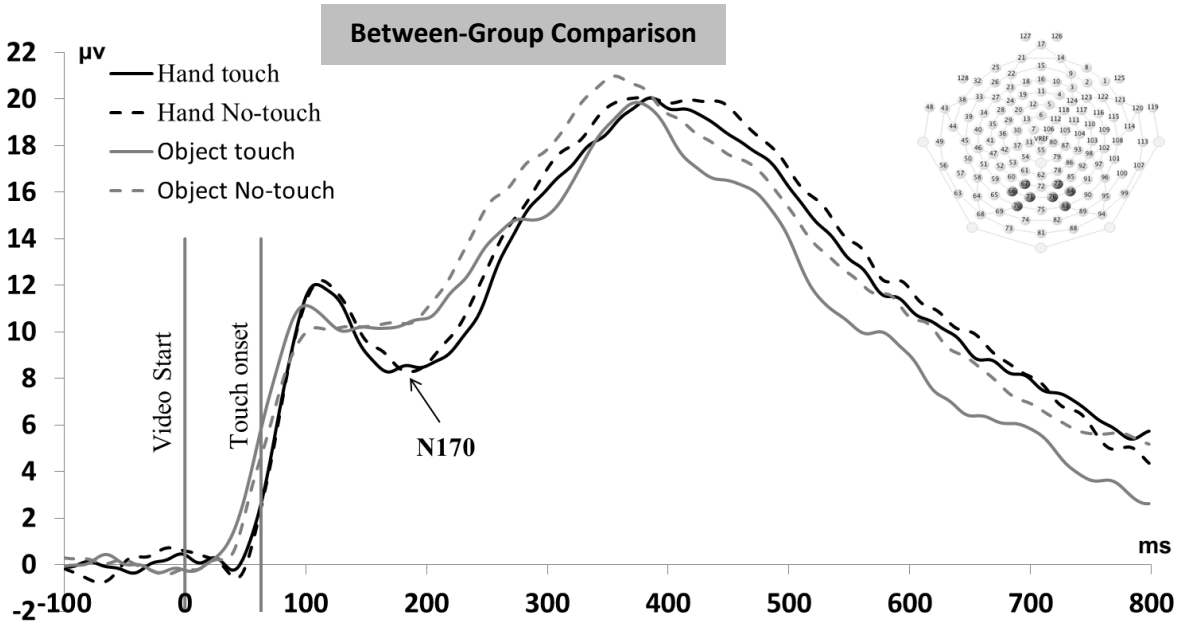

Figure 3.3. Occipital-Temporal (Visual Perceptual) Waveforms. Grand average ERP waveforms for occipital-temporal electrodes in the touch and non-touch conditions in two groups of children who observed human stimuli and objects. All components are labeled according to their timing in relation to the initial onset of the video stimulus. The latencies of peak amplitudes of the N170 component exhibited a main effect of Stimulus Type, whereby latencies were shorter for human stimuli compared to object stimuli.

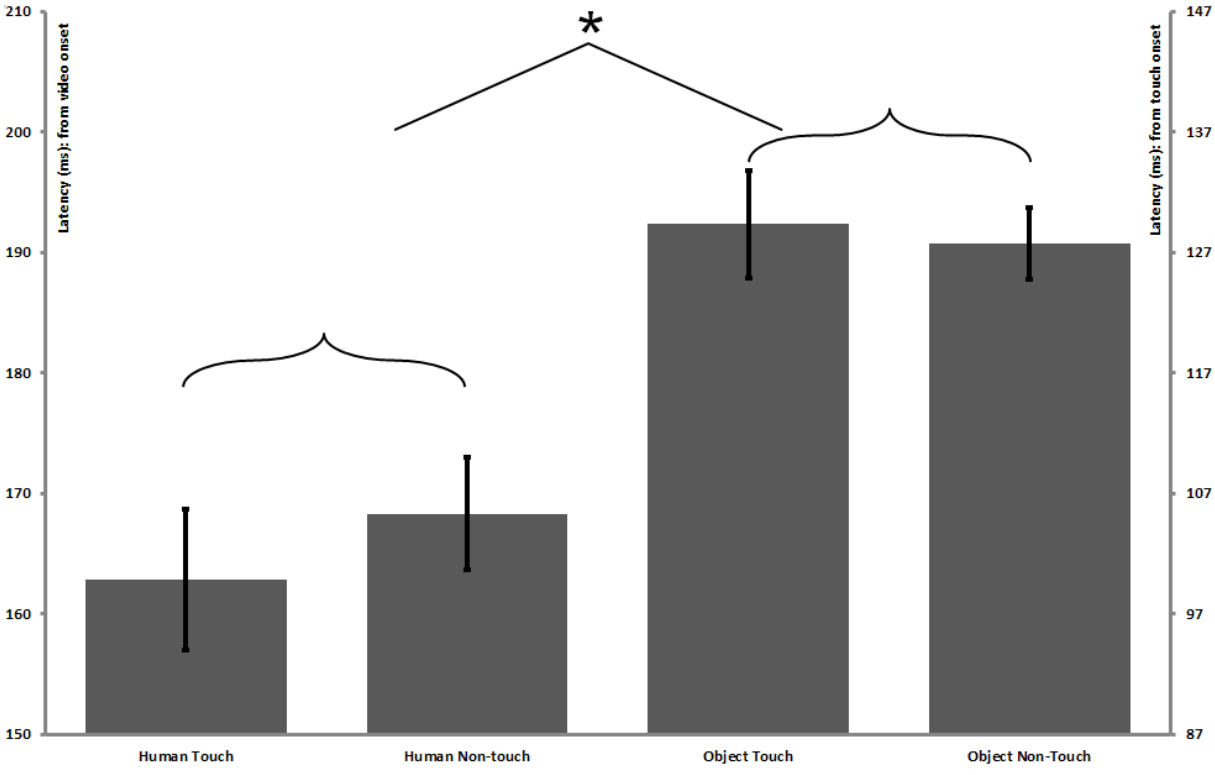

Figure 3.4. Occipital-Temporal (Visual Perceptual) N170 Latency Effects. Bar graphs present the mean (standard error) ERP latency differences for the N170 component in the occipital-temporal region. The left vertical axis presents timing in relation to the initial onset of the video stimulus, and the right vertical axis presents timing in relation to the onset of the touch within the video stimulus. A main effect of Stimulus Type indicates shorter latencies for human versus object stimuli.

Central Occipital (Visual Sensory-Perceptual) Components

A repeated measures ANOVA with Touch (Touch, Non-Touch) and Hemisphere (Left, Right) as within-subjects factors and Stimulus Type (Human, Non-Human) as a between-subjects factor revealed no significant effects or interactions observed for either the latencies or amplitudes of the occipital P100, N200 and P300 components ($F(1;38)<1$, $ps>0.1$).

Discussion

In the present study, we examined the neural correlates of touch observation in children. In particular, we utilized event-related potentials to investigate the nature and time-course of the activation of somatosensory processing mechanisms during children's passive observation of humans versus objects being touched. The primary aim of this study was to determine whether or not the brain activity of children produces evidence for tactile mirroring mechanisms during the observation of human and object touch. Using an established paradigm that allows for better and more fine-grained analysis of the time-course of activation of these mechanisms, we further examined whether or not the temporal activation of these mechanisms was similar to those in adults.

The results of the current study demonstrate that touch observation elicited different levels of activity recorded from electrodes located over somatosensory cortex at a late cognitive stage of processing during the observation of both human and non-human touch. In addition, human stimuli elicited larger amplitude activity at an early sensory-perceptual stage of processing in these same electrodes (N100). In contrast, no stimulus effects or interactions were observed in either the occipital or occipital-temporal P100 components, suggesting that the somatosensory effects were not driven by visual sensory-perceptual processing. Finally, we observed latency differences in the occipital-temporal N170 component, with shorter latencies in response to human versus non-human stimuli. Extensive previous research indicates these latter differences are likely associated with differential processing of socially relevant information (e.g., faces, bodies) versus objects in extrastriate visual areas (Rossion & Caharel, 2011). Taken together, the current findings suggest that, as in the previous study of adult participants, somatosensory mechanisms are activated both preceding and following the

perceptual encoding of the humanness of the stimuli in extrastriate regions of visual cortex during touch observation (Chapter 2: Streltsova & McCleery, 2014).

Overall, the current findings in children are in line with the previous fMRI and MEG research in adults that demonstrate the activation of the somatosensory cortex during touch observation (Keysers et al., 2004, Ebisch et al., 2008, Bufalari et al., 2007, Pihko et al., 2010). The current results are also consistent with the only existing evidence for the maturation of visuo-tactile processing mechanisms in children (Remijn et al., 2014), and extend these findings to provide evidence for somatosensory event-related potential responses during the observation of human and object touch in children. Taken together with this previous evidence in adults and children, then, the current findings suggest that somatosensory processing mechanisms are activated during both human and non-human touch observation, in 4- to 5- year old children.

To address whether the observed tactile mirroring mechanisms are relatively mature by 4- to 5- years of age, we also consider the pattern of findings of the current study in light of the results of our previous study in adults using the same ERP paradigm (Chapter 2: Streltsova &McCleery, 2014). Overall, the observed ERP effects recorded over somatosensory cortex and extrastriate visual areas, including the timings of these effects, were highly similar in these two studies. However, there are subtle differences. In particular, inconsistent with our prediction, no early (before 300 ms) touch versus non-touch ERP effects, such as those previously uncovered in the adult study, were observed in children. Instead, touch versus non-touch effects were only reflected in the amplitude effects of late slow wave component (LSW) activity at 600-700 ms over the parietal-central area, for both human and object stimuli. This indicates that touch observation mechanisms are present for both object and human stimuli, and are associated with late cognitive processing in the

somatosensory region in children. We also observed an interaction between Hemisphere and Stimulus type indicating more processing of object stimuli in left versus right hemisphere somatosensory regions, during this Late Slow Wave component. Considering that the development of tactile mirroring is a newly emerging area of research, and that our stimulus presentations were experimentally balanced across left and right hands, further neuroimaging studies need to be carried out in children in order to determine the nature and consistency of these hemispheric lateralization effects.

In addition to the LSW touch versus non-touch effects observed over somatosensory cortex, the present findings also demonstrated larger amplitude responses in the somatosensory N100 component for human relative to non-human stimuli. This finding suggests that human stimuli elicit more somatosensory activity than non-human stimuli in the context of touch observation, at an early stage of information processing. Overall, this finding is consistent with several previous findings in adults that have demonstrated the involvement of somatosensory cortex in processing social stimuli (Saxbe et al., 2012; Gazzola et al., 2012, for review see Keysers et al., 2010 and Bufalari &Ionta, 2013). Additionally, the current findings extend this research by describing the ERP time-course for touch observation. Based upon the current results and the adult literature described above, as well as the results of Chapter 2 (Streltsova and McCleery, 2014), we hypothesize that somatosensory cortex is involved in encoding of the humanness of the stimuli at an early stage of processing (N100) as well as in the encoding of touch versus non-touch processing at a later stage of processing (LSW), in children.

Despite subtle differences, overall the current results suggest a similar pattern of somatosensory activity during children's observation of touch relative to adults. This is consistent with previous studies of the development of the mirror system that have shown that the magnitude of sensory-motor alpha desynchronization during action observation was similar in 4- to 11- year old children and adults (Lepage & Theoret, 2006, see more on mu desynchronization in Chapter 4), and that the same premotor-parietal network was activated during the observation of motor acts in children as in adults (Berchio et al., 2013). The current findings make an important contribution to our understanding of mirror functioning in early childhood (see Marshall and Meltzoff, 2014) by providing further neurophysiological evidence for the overall establishment of another aspect of mirror functioning, tactile mirroring, in preschool and school-age children.

Our findings of a relatively mature mechanism for somatosensory processing of touch observation in children are also in line with a recent ERP study of face processing which demonstrated that the same visual extrastriate mechanisms were involved in the perceptual encoding of faces in 4- to 5- year old children as in adults (Kuefner et al., 2010, Bentin et al., 1996, Rossion & Gauther, 2002). On the other hand, it was shown that these same face processing mechanisms were reflected in the amplitudes and latencies of the infant N290 and P400 components, with waveform timing and topography that differ notably from those observed in adults (de Haan & Nelson, 1999, Halit et al., 2004). In future research, it will be interesting to determine whether or not the early somatosensory human versus object effects that occur by 100 ms in both children and adults using the current paradigm have a developmental trajectory as has been observed in the N290-P400 complex in infants that matures into the N170 component in adults for face processing (Halit, de Haan, & Johnson, 2003). It will also be important to examine the existence, nature, and timing of the touch

versus non-touch effects observed in the current study in infant participants in the future, as the vast majority of previous research on late cognitive and encoding mechanisms has been based solely on face processing (Nelson & McCleery, 2008).

The results of the present study have solid implications for our understanding of the mechanisms of normal cognitive and neural development associated with social mirroring, and also open up the opportunity to investigate the development of these mechanisms from birth until early childhood (e.g., Carver et al., 2003; Halit et al., 2004). The current paradigm also opens up the opportunity to examine the mechanisms and time-course of tactile mirroring in children with autism, who exhibit impairments and atypicalities in certain aspects of mirror functioning (Becchio & Castiello, 2012, Oberman et al., 2013, Enticott et al., 2012).

In summary, the current findings reflect the first examination of the existence, nature and time-course of the neural mechanisms involved in the observation of human versus object touch in children. The results provide evidence that tactile mirroring mechanisms are recruited during the observation of both human and object touch at a late cognitive stage in children. In addition, we found evidence that the somatosensory processing system responds more to the presentation of human versus object stimuli, which was reflected in larger amplitude of an early sensory-perceptual processing ERP component recorded from electrodes over somatosensory cortex. Finally, the observed ERP effects in somatosensory regions both preceded and followed the differential activity of human versus non-human objects in extrastriate visual cortical regions. Taken together, these findings demonstrate that somatosensory mechanisms for the observation of human and non-human touch are relatively developed by 4- to 5- years of age.

CHAPTER 4:

SOMATOSENSORY ALPHA AND BETA MODULATION DURING TACTILE STIMULATION IN ADULTS AND CHILDREN

Abstract

Previous research has reported suppression of alpha and beta rhythms during both the observation and execution of an action recorded over sensorimotor regions, in both adults and children. In the current study, we used EEG to further investigate the development of somatosensory activity during the passive experience of being touched and the observation of another person being touched. EEG was recorded in 4- to 5- year old children and adults as they were seated in front of the computer and their hand was touched by three different objects: a feather, a brush, and a hand massager. EEG alpha and beta power spectral density (PSD) was then computed for three experimental conditions: Rest, Touch Watch Hand (participants viewed their hand as it was touched), Touch Watch Screen (participants looked at the screen as their hand was touched). No modulation of alpha rhythm (7-11 Hz, 8-12 Hz) was observed over somatosensory cortex in either of the touch conditions compared to Rest, in either adults or children. However, beta rhythm (15- 24 Hz) PSD increased in both touch conditions compared with Rest, in adult participants only. The current study results did not provide evidence for somatosensory alpha suppression during the experience of touch in both adults and children. Additionally, the present data confirm the previous research that showed the modulation of beta rhythms during action execution in adults. Finally, the absence of beta modulation in children can be related to the methodological aspects of the present study, as well as due to a continuing maturation of somatosensory and motor related beta activity in young children.

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Introduction

Previous EEG studies have providing convincing evidence for the modulation of alpha (8-14 Hz) and beta (15-30 Hz) in sensory-motor regions during both observation and experience of different actions (Muthukumaraswamy et al., 2004, Babiloni et al., 2002, Perry and Bentin, 2009, Streltsova et al., 2010, Hari and Samelin, 1997, Hari, 2006). It has been proposed that the phenomenology of the sensory-motor alpha (mu) rhythm during action execution and observation reflects the activation of mirroring mechanisms, which presumably occurs due to the activation of neurons endowed with properties similar to those of mirror neurons discovered in the premotor and posterior parietal cortices of macaque monkeys (Di Pellegrino et al., 1992, Gallese et al., 1996, Rizzolatti et al., 1996, see Pineda, 2005, for a review).

Since the discovery of mirror neurons, the development of the sensory-motor alpha rhythm response has been examined extensively in EEG studies of infants and children. In particular, these studies have revealed sensory-motor alpha suppression during both action observation and execution in infants and children starting from approximately 8- to 12-months of age (Southgate et al., 2009, Southgate et al., 2010; van Elk et al., 2008, Nystrom et al., 2008; Paulus et al., 2012; Lepage & Theoret, 2006, Marshall et al., 2011). Results of Marshall and colleagues' study suggested that the development of the sensory-motor mu rhythm follows a similar trajectory as visual occipital alpha – from 5-6 Hz at 6 months, reaching a peak of 9-10 Hz of adult frequencies by approximately 4 years of age (Marshall et al., 2002, 2011). These data were also confirmed by the findings of a study by Lepage and Theoret showing mu desynchronization in 4- to 11-year old children during the observation and the execution of a precision grip (Lepage & Theoret, 2006).

In addition, Southgate and colleagues showed the presence of mu desynchronization in 9 month old infants during both action observation and the execution of a goal-related action such as grasping and reaching (Southgate et al., 2009). Southgate and colleagues also found that mu desynchronization occurred for both visible and occluded stimulus conditions, suggesting that infants' motor system can extract goals from the non-visible actions (Southgate et al., 2009). Another EEG study showed a higher desynchronization for goal-related action than for a similar non-goal related action, suggesting that some aspects of the mu desynchonization are sensitive to goals (Nystrom et al., 2011). Additionally, van Elk and colleagues found stronger alpha and beta desynchronisation during the observation of crawling videos compared to walking videos (van Elk, 2008; for review, see also Vanderwert, Fox, Ferrari, 2013), suggesting that the mu rhythm is sensitive to the level of experience the infants had with actions or their goals.

In addition to modulation of the alpha rhythm over cortical sensory-motor regions, it has also been observed that modulation of low and high beta (15-30 Hz) frequencies is linked to action perception and production (Gaetz and Cheyne, 2006, Hari and Salmelin, 1997). However, the specific role of beta rhythms in action processing is still debated (Quandt et al., 2013). For example, although alpha and beta rhythms have similar characteristics related to action processing, there is some evidence for their functional differences and different cortical origin (Shao et al., 2012). The results of neuroimaging studies have suggested that sensory-motor alpha rhythm modulation is associated with activity in the primary somatosensory cortex (Arnstein et al., 2011, Ritter et al., 2009). In contrast, the results of MEG studies have suggested that beta rhythm modulation originates in the precentral gyrus of the motor cortex (Hari and Samelin, 1997, Samelin and Hari, 1994). Most relevant to the current study, the development of sensory-motor event-related beta desyncronization (ERD) and

synchronization (ERS) identified in adults has only been addressed in a very small number of studies in children. A recent MEG study showed that movement related beta oscillations occurred in the sensory-motor area in children but they had different properties, specifically, different timing and stronger frequency band coupling, compared to that in adults (Cheyne et al., 2014). Additionally, a recent EEG study examined spontaneous EEG of over one hundred participants between 6 and 26 years of age (Rodríguez-Martínez et al., 2014). The findings suggested the co-maturation of the power spectral density (PSD) of spontaneous EEG rhythms from theta (4-7 Hz) to gamma (25- 80 Hz) bands, presumably due to maturational changes in neural tissues underlying these particular frequencies. Taken together, the previous findings suggest the continuing maturation of spontaneous EEG rhythms, as well as movement related beta rhythms, over the central region in children.

A newly emerging area of the research is the development of touch processing mechanisms. Behavioural research of touch processing demonstrated that although among all sensory functions touch is the earliest to develop (Pihko and Lauronen, 2004, Bartocci et al., 2006), some features of tactile perception continue to develop later in childhood. For example, tactile acuity in tactile grating orientation task increased with age in cross-sectional study of participants from 6- to 16- years of age (Peters and Coldreich, 2013). Additionally, it was found that accuracy in all validated measures of somatosensation, which include haptic recognition, touch detection-discrimination, and proprioreception improved from children of 3 years of age until adolescence (Dunn et al., 2015). A recent longitudinal neuroimaging study investigated brain responses to touch of palm and forearm in children, adolescents and young adults (Björnsdotter et al., 2014). The results of this study suggested that brain mechanisms associated with processing of sensory (somatosensory cortices) and emotional (insular cortex) aspects of touch are largely established in school-age children (Björnsdotter

et al., 2014). Additionally, Xiang and colleagues investigated neuromagnetic activities induced by finger stimulation (Xiang et al., 2004). The results of this study provide the somatosensory activation map data indicating the differences between the somatosensory maps in children from 3- to 6- years of age and adults. In particular, the thumb functional area was found to be larger than that of the middle finger in children (Xiang et al., 2004). A developmental aspect of touch processing, accompanied by touch observation, was also addressed in a recent MEG study that showed that the observation of tactile finger stimulation modulated the somatosensory activity produced by finger touch in 3- to 4- year old children (Remijn et al., 2014). The results of this study showed a somatotopic organization of the electromagnetic response during tactile stimulation accompanied by the observation that further suggests the maturation of tactile processing mechanisms at early age. Together, these results suggest maturation of some aspects of somatosensory processing (responses to touch, somatosensory cortex) and ongoing development of other aspects, such as tactile discrimination and acuity and somatosensory activation maps, in preschool children. However, there is no further neurophysiological evidence for the development of touch processing mechanisms in preschool and school-aged children.

In the current study, we used EEG methods to further explore somatosensory activations during tactile stimulation, and the development of touch processing mechanisms. The current study represents a follow-up to the previous ERP studies, where we examined similar somatosensory modulation which occurred during the observation of human and object touch in adults (Chapter 2: Streltsova & McCleery, 2014) and in children (Chapter 3). The aim of the current study was to further explore the modulation of somatosensory alpha activity during the experience of touch in both adults and children. This study was conducted on the same adult participants as our previously published ERP study (Chapter 2: Streltsova

& McCleery, 2014), and the same children that took part in the ERP study in Chapter 3. In the current study, we applied time-frequency EEG analysis methods, in an effort to specifically determine whether neural activations similar to those found in somatosensory areas during ERP studies (e.g., Chapter 2: Streltsova & McCleery, 2014, Chapter 3) are also present during tactile and visual-tactile stimulation conditions. In order to examine and compare brain activations at two time-points in development, the same procedure was employed for adults and young children. Based upon previous EEG studies of action observation in adults and children (Muthukumaraswamy et al., 2004, Perry and Bentin, 2009, Streltsova et al., 2010, Lepage and Theoret, 2006, Quandt et al., 2013), we predicted that modulation will be present in somatosensory alpha band (8-12 Hz) and beta bands (15-24 Hz) in both adults and children, and will not differ between the groups. Based on the previous EEG/MEG findings showing modulation of somatosensory activity during tactile stimulation by the observation of touch in adults and children (Bufalari et al., 2007, Martinez-Jauand et al., 2012, Remijn et al., 2014), we also predicted that modulation would be the greatest in the visual-tactile condition (Touch Watch Hand), where the participants looked at their hand while it was touched, compared to the condition where the participants had to look away from their hand (Touch Watch Screen).

Methods

Participants

The adult participants were 13 undergraduate students (10 female, 3 male) from the University of Birmingham. Participants' mean age was 21 (range: 18-26). Child participants were 17 (7 female, 10 male) 4- and 5- year-old children from the city of Birmingham and

surrounding districts, in the West Midlands region of the United Kingdom. Children had a mean age of 55 months (range: 50-69 months). Data from an additional 3 adult participants and 20 child participants were excluded as they produced less than 20 sec of artefact free data per condition. All adult participants reported that they had no history of a neurological or psychiatric disorder, and they had normal or corrected to normal vision. Additionally, the parents of all child participants reported that their child had no history of a neurological or psychiatric disorder and had normal or corrected to normal vision. All included adult participants were right-handed and all parents of participating children reported them as being right-handed. Informed written consent was obtained from all adult participants and parents of all child participants prior to participation in the study, in accordance with an ethical protocol approved by the Ethical Review Committee of the University of Birmingham.

Procedure

Participants were seated comfortably in an isolated sound-attenuated EEG testing room in front of the computer stimulus monitor. The EEG was recorded in the following conditions: Rest, Touch Watch Screen and Touch Watch Hand. The conditions were always presented in the same order: Rest, followed by Touch Watch Screen and then followed by Touch Watch Hand. The duration of the recording was one minute for Rest conditions and two minutes for Touch conditions, with one minute allowed for each hand. The experiment started with the Rest condition where the participants were asked to relax while watching the grey screen with a fuzzy movement. Following this, during Touch Watch Screen conditions participants were told to keep looking at the same screen while the experimenter touched both hands with three objects in a different order: a peacock feather, a brush and a gentle hand

massager. Following this, during Touch Watch Hand participants were asked to look at their hand while the experimenter continued touching it, and the EEG recording continued for another two minutes. The participants received a gentle touch on their palm and glabrous part of the forearm with all of the three objects. The order of the hands and the order of objects was counter-balanced across the participants. The experimenter counted the number of tactile movements performed with each object and the duration of the touch which was about one second per movement. The experiment took place in a sound-attenuated, dimly lit room, and the stimuli were presented on a 17-inch computer monitor with a viewing distance of 80 cm. A miniature digital closed-circuit video camera located below the stimulus presentation monitor was used in vivo by an experimenter to identify and mark any trials during which participants were not attending to the screen in Touch Screen conditions.

EEG recording and data analysis

EEG data were acquired using a 128-channel Hydrocel Geodesic Sensor Net (HCGSN) and recorded with NetStation 4.3.1 software (Electrical Geodesic, Eugene, Oregon). EEG was sampled at 500 Hz, and electrode impedances were kept below 80 KOhm in adult participants and 100 KOhm in children. Raw EEG data were recorded with the vertex (Cz) as the online reference and re-referenced off-line to an average reference. Stimuli were presented using E-Prime 2.0 software (Psychology Software Tools) which, at the start of each condition, sent all event markers to NetStation.

The raw EEG files were filtered with 0.1 Hz high pass filter and 50 Hz Notch filter in NetStation 4.4.1 and then segmented according to the conditions. Data were then processed using an artifact detection tool that marked channels bad if the recording was poor for > 20%

of the time (amplitude threshold (max – min) >100. Bad channels in the EEG data were replaced using a spherical spline interpolation algorithm (Srinivasan et al., 1996). The EEG files were then visually inspected and the segments with more than 2 seconds of artefact free data were selected manually and kept for further analysis. Video camera recording was used to identify the segments where participants looked at their hand in Touch Watch Screen conditions. These segments were excluded from the further analysis. The segmented EEG files were exported in .raw files and all further analysis was performed in Matlab (MATLAB 2014, Mathworks, Inc., Massachusetts, USA). The participants who produced less than 20 sec combined good segment data per condition were excluded from further analysis. After exporting data to Matlab, each dataset was referenced to an average reference. Then the Fast Fourier Transformation (FFT) was performed for each segment of the EEG data separately for the adult and child participants. The frequency-power coefficients were calculated for the alpha (7-11 Hz – children (Saby & Marshall, 2012, Marshall et al., 2002, 8-12 Hz –adults) and beta frequency (15-24 Hz) bands for each segment. Considering that relatively little is known about developmental changes in sensory-motor and somatosensory alpha and beta oscillations (Marshall et al., 2011, Cheyne et al., 2014), adult and child PSD graphs were computed and further examined, and peaks corresponding to somatosensory alpha and beta oscillations were identified (see **Figure 4.2**). Additionally, previous research examining movement related activity in adults and children suggested that beta power changes are reflected in narrower frequency bands in children than in adults (Jurkiewicz et al., 2006, Cheyne et al., 2014). Based on the presence of the peaks of beta oscillations in PSD graphs, two intervals representing ‘low’ and ‘high’ beta bands were selected for further analysis in children: 15-20 Hz and 21-24 Hz, while the whole beta range (15-24 Hz) was analysed in adults.

The purpose-built Matlab program was based on one created by Grieve and colleagues (2008), as the authors found that this program produced statistically reliable PSD measurements and interhemispheric coherence. In accordance with Grieve and colleagues' methodology (Grieve et al., 2008), Matlab program used in the current study split the EEG data into one second epochs. The FFT was performed for each epoch of the data using Welch method with 500 ms Hamming window and 60 % overlap. The FFT values for each segment in Rest condition, Touch Watch Screen and Touch Watch Hand conditions were then averaged and exported to SPSS. After that, the FFT values in each condition were extracted from the central somatosensory area that included the same electrodes as in the ERP study (Chapter 2: Streltsova & McCleery, 2014) (see electrode locations in **Figure 4.1**). A 3x2 repeated measures ANOVA with three factors of Condition (Rest, Touch Watch Screen, Touch Watch Hand) and two factors of Hemisphere (Left, Right) was performed for the central electrode montage (see **Figure 4.1**) separately for adult and child participants. Paired-sample t-tests were performed to further explore significant main effects and interactions. Bonferroni corrections were employed for all post-hoc paired sample comparisons.

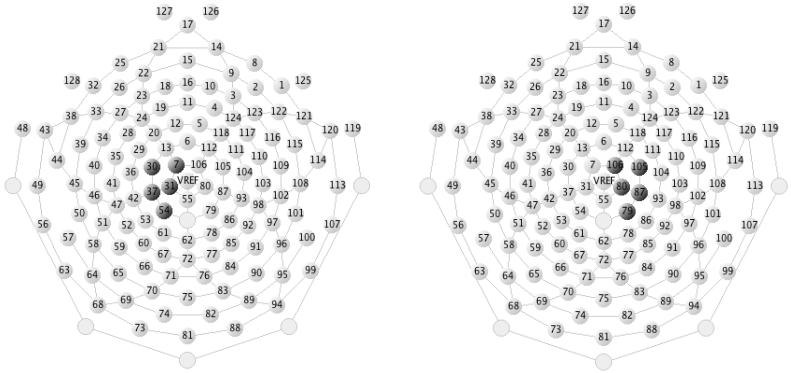
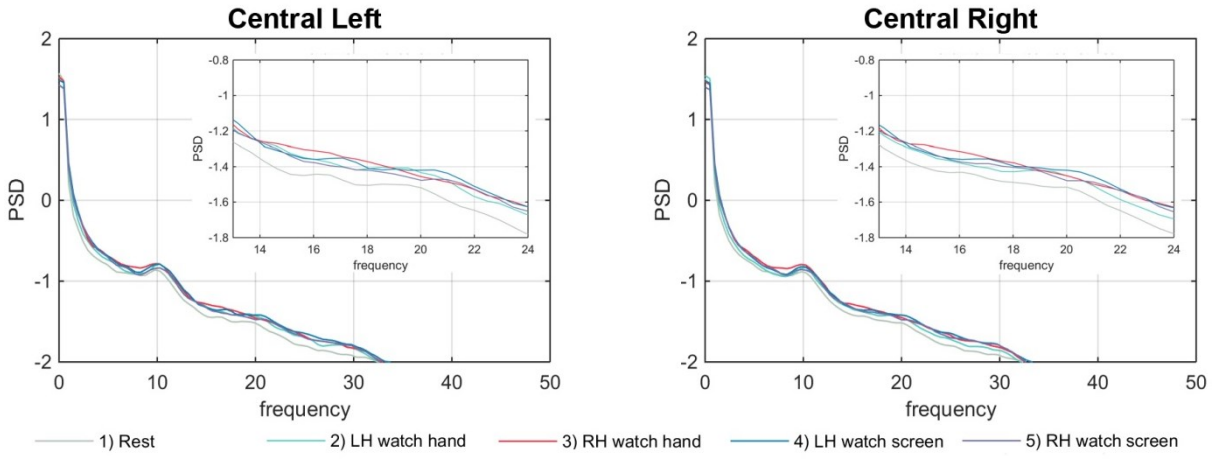


Figure 4.1. **Location of the electrodes**. Electrodes selected for the analysis in the central (somatosensory) area.

4.2 A



4.2 B

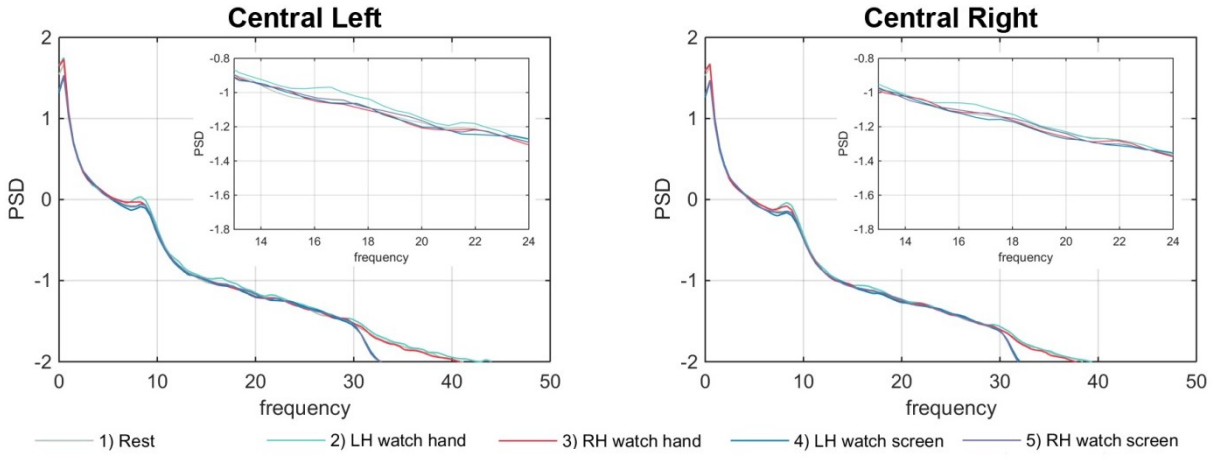


Figure 4.2. **Power spectral density graphs in the central area.** PSD graphs in the central (somatosensory) area in the four experimental conditions in adult (A) and child (B) participants.

Results

Adult participants

Alpha activity

No main effect of Condition was revealed in the central area ($F(2;24)=1.4$, $p>0.1$). The PSD values for the alpha activity in each condition in adults are shown in **Figure 4.3a**.

Beta activity

A repeated measures ANOVA with three factors of Condition (Rest, Touch Watch Screen, Touch Watch Hand) and two factors of Hemisphere (Left, Right) revealed a significant main effect of Condition in the central region ($F(2;24)=6.9$, $p<0.01$). The post-hoc paired sample t-tests identified the increase of beta PSD in the Touch Watch Screen condition compared to Rest (MD=0.097, S.E.=0.032, $p<0.05$), as well as the increased beta activity in Touch Watch Hand condition compared to Rest (MD=0.1, S.E.=0.035, $p<0.05$) (see **Figure 4.4a**).

Child participants

Alpha activity

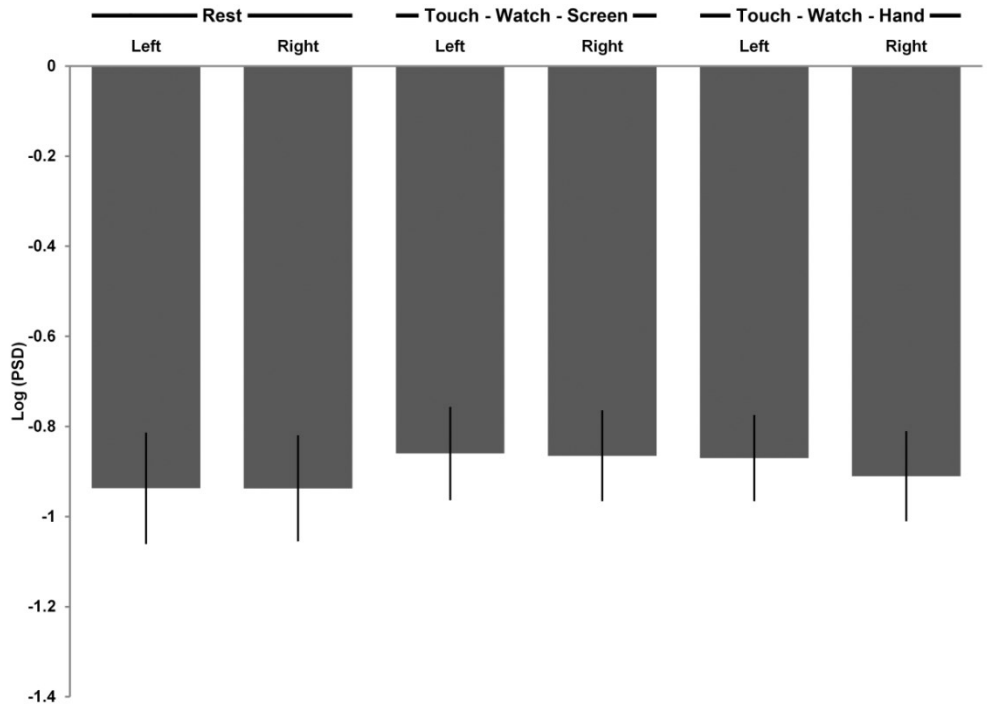
There was no significant main effect of Condition revealed in the central area ($F(2;32)=1.5$, $p>0.05$). However, the main effect of Hemisphere ($F(1;16)=4.6$, $p<0.05$) and the interaction between Condition and Hemisphere ($F(2;32)=3.3$, $p=0.05$) were significant. The post-hoc comparison t-tests showed that the interaction was driven by the difference between Touch Watch Screen and Touch Watch Hand in the left hemisphere, with greater

alpha PSD in the Touch Watch Hand condition over the left hemisphere (MD=0.09, $p<0.05$). The difference between Rest and the Touch conditions was not significant ($p=0.2$). The PSD values for the alpha activity in each condition in children are represented in **Figure 4.3b**.

Beta activity

A repeated measures ANOVA with three factors of Condition (Rest, Touch Watch Screen, Touch Watch Hand) and two factors of Hemisphere (Left, Right) did not reveal a significant main effect of Condition, or significant interaction ConditionxHemisphere in the central region for the both 15-20 Hz and 21-24 Hz frequency bands (Condition: $F(2;32)=0.4$, $p>0.1$, $F(2;32)=0.2$, $p>0.1$; ConditionxHemisphere: $F(2;32)=0.2$, $p>0.1$, $F(2;32)=0.1$, $p>0.1$). The main effect of Hemisphere was significant for the both frequency bands ($F(1;16)=7.6$, $p<0.05$, $F(1;16)=8.2$, $p<0.05$). The PSD values for the beta activity in the central region, for the ranges 15-20 Hz and 21-24 Hz of beta band in children are shown in **Figure 4.4b** and **Figure 4.4c**, respectively.

4.3 A



4.3 B

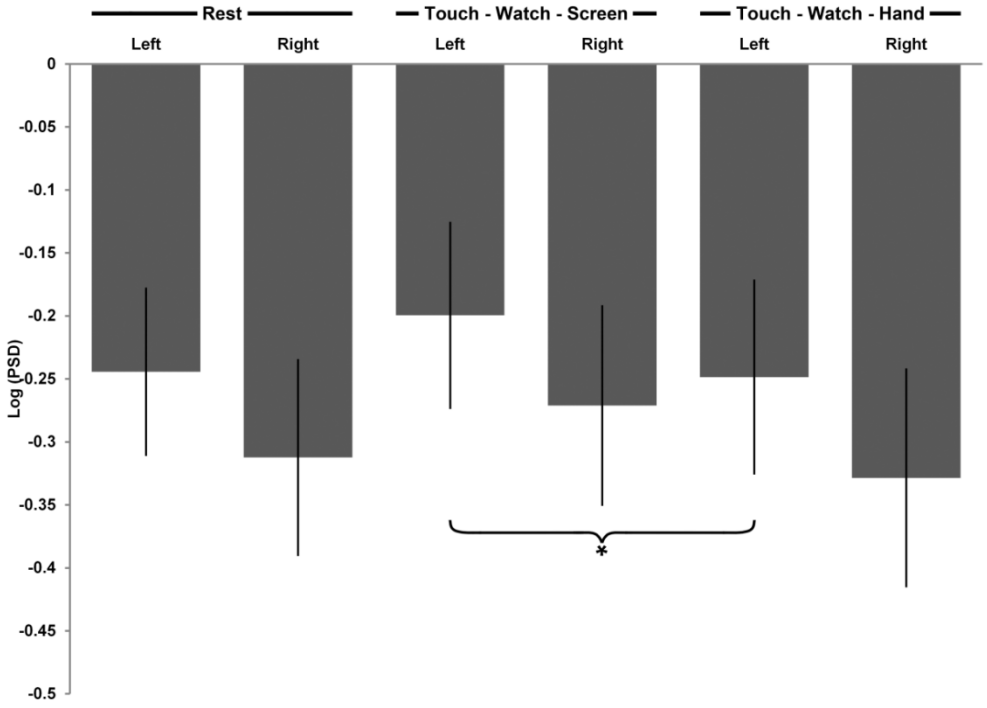
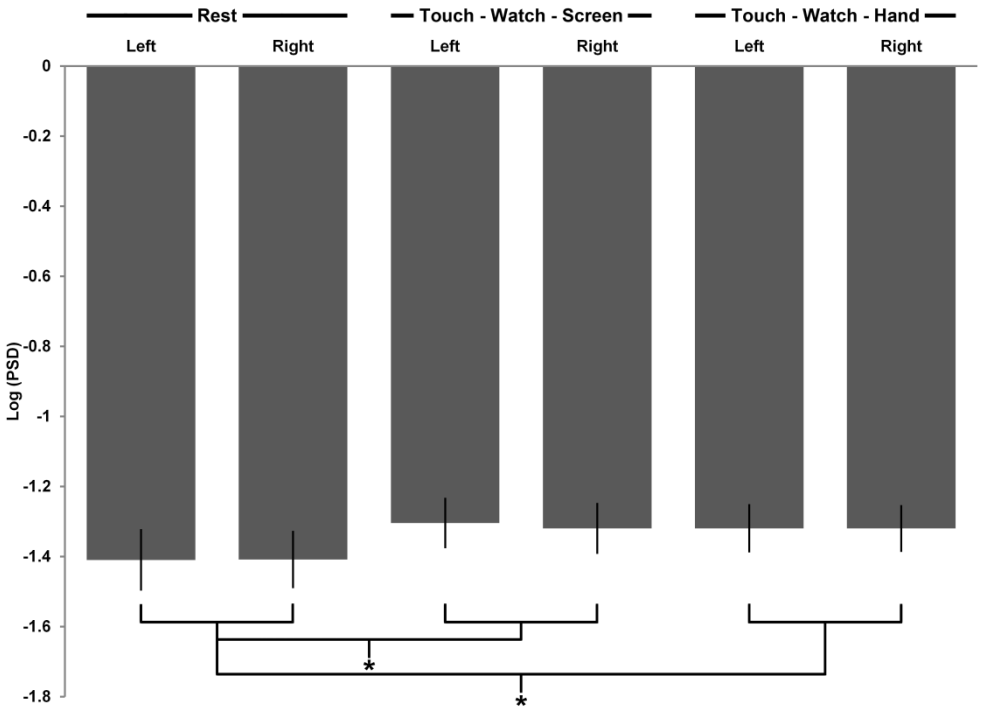
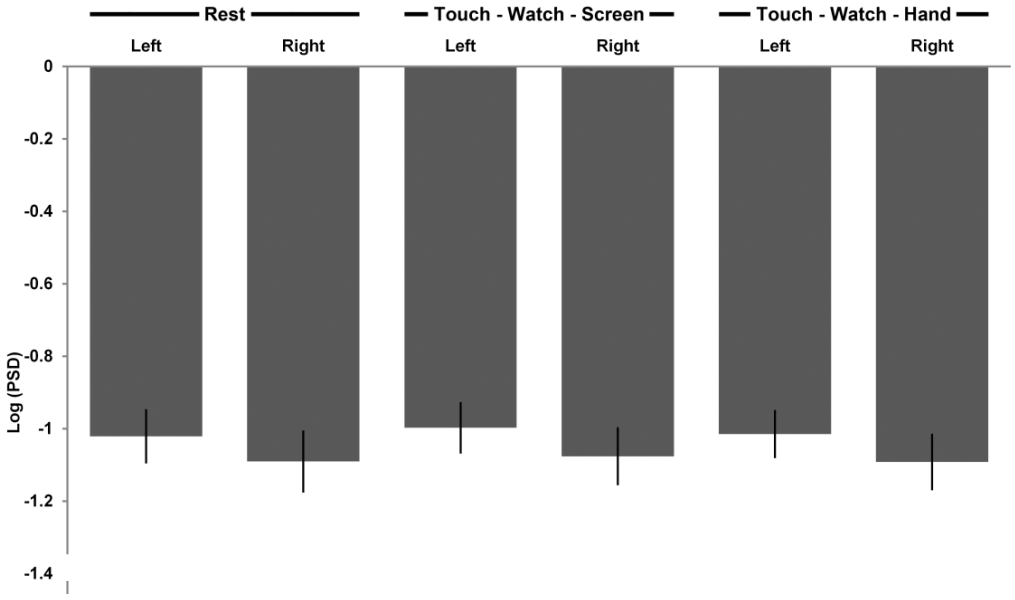


Figure 4.3. Somatosensory alpha modulation in adults and children. The figure represents the logarithm of the power spectral density (PSD) of the alpha rhythm in the somatosensory (central) area in adult (A) and child participants (B).

4.4 A


Rest
Touch - Watch - Screen
Touch - Watch - Hand
Left
Right
Left
Right
Left
Right
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
-1.8
Log (PSD)
*
*

4.4 B


Rest
Touch - Watch - Screen
Touch - Watch - Hand
Left
Right
Left
Right
Left
Right
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
Log (PSD)

4.4 C

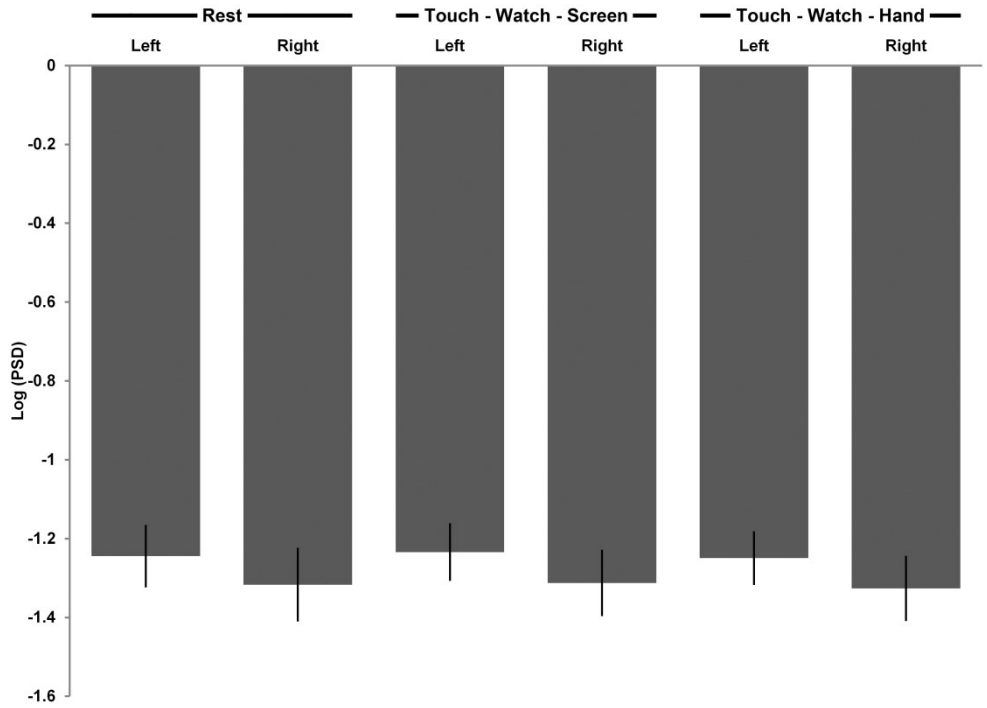


Figure 4.4. Somatosensory beta modulation in adults and children. The figure represents the logarithm of the power spectral density (PSD) of the beta rhythm in the somatosensory (central) area in adult (A) and child participants for 'low' beta (15-21 Hz) (B) and 'high' beta (21-24 Hz) ranges (C).

Discussion

In the current study, we used EEG methods to investigate the modulation of somatosensory alpha and beta modulation during tactile stimulation in adults and children. In particular, we examined the development of somatosensory modulation using the same paradigm in adults and in children aged 4- to 5- years. The present results revealed the modulation of beta (15-24 Hz) rhythms in the somatosensory area in both touch conditions in adult participants. Specifically, we found the increase of beta activity in adults in the central area, which might be similar to "beta rebound" previously localized to a motor cortex (Hari, 2006, Gaez & Cheyne, 2006; Jurkiewicz et al., 2006). It is worth noting that the previous

results on adult beta ERS/ERD during movement and tactile stimulation are rather mixed and very little evidence is present in children. For example, there is some evidence showing the beta rhythm desynchronization in a response to tactile stimulation in adult participants (Avanzini et al., 2012, McFarland et al., 2000, van Ede et al., 2012). However, there is also evidence for the synchronization in beta band in response to tactile stimulation (Cheyne et al., 2003, Neuper and Pfurtsheller et al., 2001, Pfurtscheller et al., 2001). In sum, our findings are in line with the abovementioned findings showing beta synchronization in adults. Notably, the increase of beta activity in the central area was absent in 4- to 5- year old children. Interestingly, a previous neuroimaging study showed that a post-movement "beta rebound" was significantly reduced in children from 4- to 6- years of age (Gaetz et al., 2010). It was suggested this reduction might reflect a decrease in motor cortical inhibition, which might facilitate motor learning in children (Gaetz et al., 2010).

It is worth noting that the increase of beta activity was found in both touch conditions – tactile condition (participants looked away from their hand) and visual-tactile conditions, in which participants looked at their hand while it was touched. Despite the evidence for sensory-motor alpha and beta modulation, there is little previous EEG and MEG evidence to demonstrate the modulation of beta rhythms during the observation of somatosensory experiences. One MEG study reported the desynchronisation of both alpha and beta rhythms during tactile stimulation followed by the "beta rebound" in sensorimotor regions (Cheyne et al., 2003). Their findings also showed increased beta activity in the sensory-motor regions during the observation of touch. Additionally, a recent EEG study demonstrated increased beta activity during the observation of an action that was expected to result in somatosensory stimulation (Quandt et al., 2013). It has been suggested that observation of an action recruits not only the premotor or motor areas but also area BA 2 and SII which are involved in

processing sensory aspects of an action, including how our body would interact with an object (Keysers et al., 2010). Other studies also showed that somatosensory experiences can contribute to the sensory-motor activations during action observation (Cheyne et al., 2014; Quandt et al., 2013). Interestingly, a recent EEG study investigated the effect of the repetition of tactile or motor features of actions on the sensory-motor alpha suppression in adults (Coll et al., 2015). The results suggested that sensory-motor alpha suppression was sensitive to tactile rather than motor properties of an action (Coll et al., 2015). Additionally, previous MEG and fMRI research suggests localization of the sensory-motor alpha to the primary somatosensory cortex (Hari et al., 1997, Cheyne et al., 2003, Ritter et al., 2009). Taken together, the current findings contribute to the previous research demonstrating the modulation of somatosensory activity in beta (15-24 Hz) frequency band during tactile stimulation alone, and tactile stimulation accompanied by the observation of touch.

It might be possible that beta ERS found in the current study is potentially related to a "beta rebound" phenomenon that usually occurs after movement. It is worth noting that the gaps between the tactile movements were short and presumably were included in the FFT analysis. In contrast to previous SEP studies (Bufalari et al., 2007, Remijn et al., 2014, Martinez-Jauand et al., 2012) where an onset of stimulation and of somatosensory responses are defined very clearly, somatosensory synchronization/desynchronization might represent the activity that occur sometime after stimuli. Therefore, it might be possible that the somatosensory beta ERS and ERD were mixed in the FFT analysis, in the current study. Finally, although we intended to include the central electrodes situated over primary somatosensory cortex, due to the low spatial resolution of the EEG technique, it is possible that the EEG at this location partially included the rhythms that originated in the primary motor cortex. Consistent with this notion, it has been suggested that alpha and beta rhythms

have different activity sources originating from the somatosensory cortex and motor cortex, respectively (Hari et al., 1997, Cheyne et al., 2003). Thus the beta synchronization found in the current study could potentially reflect a 'beta rebound' occurring during the tactile stimulation.

In contrast to previous MEG and EEG findings showing the modulation of sensorimotor alpha activity during action execution and observation in adults and children (Muthukumaraswamy et al., 2004, Perry and Bentin, 2009, Streltsova et al., 2010, Lepage and Theoret, 2006), we did not observe evidence for suppression of somatosensory alpha in either of two separate Touch conditions compared with Rest. This finding was consistent across the adult and child participants in our study. However, we did observe an increase in alpha activity in the Touch Watch Hand compared to Touch Watch Screen condition in the left hemisphere only, in children. This finding contradicts our initial hypothesis, in that we hypothesized more alpha suppression would be observed in the visual-tactile Touch Watch Hand condition compared with the Touch Watch Screen condition, due to the increased modulation of somatosensory activity during the observation of touch, accompanied by tactile stimulation (Bufalari et al., 2007, Martinez-Jauand et al., 2012, Remijn et al., 2014). It is worth noting that the posterior alpha modulation usually occurs in the similar frequency band (8-14 Hz) as central alpha (mu) frequency band (for review, see Pineda, 2005). Additionally, there was a significant variation in visual stimulation between Touch Watch Hand and Touch Watch Screen conditions. Specifically, in Touch Watch Hand condition, participants were required to look at their hand while it was touched when sitting in a dark room. Therefore, it might be possible that the observation of their hand exhibited more posterior alpha activity, in comparison to Rest and Touch Watch Screen conditions, in which participants were looking at brighter stimuli, such as a grey fuzzy screen. Therefore, we suggest that the increased alpha

PSD in the visual-tactile Touch Watch Hand condition might be driven by the increase of posterior alpha in this particular condition.

There are several possible interpretations for the lack of the somatosensory alpha suppression in the current study. First, to date no study has examined somatosensory alpha suppression in adults and children by applying EEG time-frequency methods. It might be possible that somatosensory effects found in previous SEP studies in adults and children (Bufalari et al., 2007; Remijn et al., 2014, Martinez-Jauand et al., 2012) are simply not reflected in the alpha frequency band. Second, an overlap between occipital and central alpha modulation might have masked the somatosensory alpha activity. Another possible interpretation is that the touch procedure employed in the current study may not have been effective enough to induce somatosensory alpha effects. Majority of the previous EEG/MEG studies investigating touch processing in adults and children utilized an induced tactile stimulation, such as an electrical stimulation delivered to a wrist or a finger (Bufalari et al., 2007, Remijn et al., 2014) or by means of a pneumatic stimulator attached to the body surface (Martinez-Jauand et al., 2012). In the current study, three different objects were used interchangeably and it was not possible to synchronize the timing of touch precisely with the EEG, suggesting that the onset and offset of touch were not determined very accurately in the data analysis. Therefore, the epochs when touch was not present might have been taken in the analysed segments. It might also be possible that variation in touch stimuli (feather, brush, massager) added some noise to the EEG data when examining somatosensory processing mechanisms. Additionally, it is known that the glabrous part of the palm contains less tactile afferent receptors than the hairy part of the hand (Rolls, 2010). This means that stimulation of the back of the hand and outer forearm would generally be more successful in triggering somatosensory effects associated with touch. Taken together, practical difficulties of the

touch procedure, the presence of variation in tactile stimuli as well as possible modulation in the occipital alpha between the conditions might have contributed to the lack of somatosensory alpha suppression effects in the current study.

The current results, together with the results of the previous chapters, contribute to the previous fMRI evidence suggesting the existence of tactile mirroring mechanisms in adults (Keysers et al., 2004, Schaefer et al., 2006, Schaefer et al., 2009; Ebisch et al., 2008, Ebisch et al., 2011), by demonstrating the modulation of somatosensory activity during tactile stimulation and the observation of touch in adults (Chapter 2) and children (Chapter 3). The current results also revealed that the increase of beta activity in the somatosensory area was absent in children. One possible interpretation is that somatosensory and movement related beta rhythms are not very well developed yet in preschool children. In line with this, the results of a recent MEG study showed that children under five years of age have different patterns of movement-related brain activity, reflected in different timings of sensory-motor alpha and beta modulation and a stronger frequency band coupling, in comparison to older children and adults (Cheyne et al, 2014). Additionally, a recent longitudinal EEG study investigated the power spectral density between theta and gamma bands in children, adolescents and young adults. It was suggested that the decrease of the PSD in these frequencies during childhood might be due to the maturation of neural tissues underlying different frequency sources (Rodríguez-Martínez et al., 2014). Taken together, the current findings support the notion that some maturational changes occur in frequency PSD measuses in childhood, by demonstrating the lack of somatosensory beta synchronization in preschool children.

On the other hand, the current results seem to contradict the fact the tactile processing mechanisms are developing prenatally and present already at birth (Bartocci et al., 2006). It is

worth noting though that frequency PSD measured in the somatosensory area is one of many possible measures which reflect cortical tactile processing. It could be possible that this particular measure continues to mature into adolescence along with other measures such as tactile acuity or somatosensory functional areas (Xiang et al., 2004, Peters and Coldreich, 2013) while other behavioural and neurophysiological measures, such as responses to touch and neurofunctional maturity of somatosensory regions are established very early in life (Kida & Shinohara, 2013). Thus, the current results should not be perceived as showing immaturity of tactile processing in preschool children, but rather indicating a continuing development of one particular measure of tactile processing in this group. However, in light of several methodological limitations, another methodology related explanation of the absence of alpha and beta ERD/ERS effects in children should also be considered (see more on study limitations below and in Chapter 6).

Study limitations and conclusions

In sum, the current findings provide further evidence for the beta activity modulation during tactile stimulation in adults. These findings shed more light on the development of beta modulation during tactile stimulation and the observation of touch in young children. One limitation of the current study is the lack of the localization of central beta activity. Taking into account the existing evidence (Hari, 2006, Gaez and Cheyne, 2006), the sources for the somatosensory beta modulation effects are likely to be generated in the primary motor cortex. In future studies, it would be interesting to address this issue by utilizing EEG source estimation techniques. It is also worth considering using another or a second baseline since central alpha (mu) and beta modulation measures are largely dependent on the baseline choice

in infant and child studies (for a review, see Cuevas et al., 2014). Specifically, introducing separate rest condition baselines for the comparison with touch segments consisting of stimulation left and right hands separately can bring more about whether the present results might be baseline dependent. Finally, it is worth mentioning that in the current study we looked at the average somatosensory activity induced by the tactile stimulation of both left and right hands, since there was not enough data to investigate ERD/ERS induced by left and right hand stimulation separately. Since a significant interaction between Condition and Hemisphere, and a main effect of Hemisphere were found in children, in future research it might be important to explore the beta modulation induced by touch delivered to right and left hand separately.

In contrast to previous findings, the current results did not show the somatosensory alpha suppression in either adults or children. Firstly, it would be important to increase the artefact free data in each condition, for both adults and children, to see whether we would get a reliable alpha suppression effect. It is also likely that somatosensory alpha activity identified in the current study was influenced by the occipital alpha activity. Therefore, in future studies it might be necessary to apply the EEG source estimation techniques, in order to distinguish somatosensory activity from the posterior activity induced by visual stimulation in tactile and visual-tactile conditions. As mentioned earlier, it might also be interesting to explore the somatosensory modulation induced by tactile stimulation of a hairy part of forearm that contains more afferent receptors (Rolls, 2010). Embedding different experimental designs as well as using tactile markers for the synchronization of tactile stimulation with EEG, such as those utilized in previous SEP studies (Bufalari et al., 2007; Remijn et al., 2014, Martinez-Jauand et al., 2012), might be potentially addressed in future research.

In future studies, it might be also interesting to employ a similar design to explore the somatosensory activation during tactile stimulation in individuals with neurodevelopmental disorders, such as autism and attention deficit hyperactivity disorder (ADHD). There is some recent evidence suggesting impaired tactile processing and diminished response to affective and neutral touch in adults and children with ASD and ADHD (Cascio et al., 2012, Cascio, 2013, Puts et al., 2014, for a review, see Cascio et al, 2010). Additionally, the results of previous EEG studies demonstrated a lack of the mu rhythm suppression during action observation in individuals with autism suggesting the impairment of mirror functioning in ASD (Oberman et al., 2005, Bernier et al., 2007; for a review, see Becchio & Castiello, 2012). In future research, it might be interesting to utilize the EEG methods used in the current study, and the ERP methods used in Chapter 2 and Chapter 3, to further explore the development of the tactile processing as well as tactile mirroring mechanisms in adults and children with autism.

To the best of our knowledge, this is the first study to employ the time-frequency EEG methods to examine the somatosensory alpha and beta modulation in adults and children. The current results demonstrate that the beta (15-24 Hz) modulation during touch, more specifically, the increase of beta PSD in the somatosensory area in adults. Additionally, this effect was absent in 4- to 5- year old children. The current findings shed more light on the development of tactile processing in young children, which was previously limited to a few findings of event-related EEG and MEG studies (Rigato et al., 2014, Gondo et al., 2001, Xiang et al., 2004; Gaetz et al., 2008; Pihko et al., 2009) and have been discussed in light of methodological limitations. More specifically, the absence of alpha modulation in both groups and beta modulation in children can be both methodology related and/or due continuing maturation of beta (15-24 Hz) cortical activity in 4- to 5- year old children.

CHAPTER 5:

NEURAL MECHANISMS OF SPEECH VERSUS COMPUTERIZED SPEECH PERCEPTION IN TYPICALLY DEVELOPING CHILDREN AND CHILDREN WITH AUTISM SPECTRUM DISORDERS

Abstract

Previous event-related potentials (ERP) research utilizing oddball stimulus paradigms suggests diminished response to speech stimuli, as well as atypical processing of some aspects of non-speech sounds in children with Autism Spectrum Disorder (ASD). In the current study, we utilized a paired repetition paradigm without the use of oddball stimuli, in order to investigate ERP responses associated with auditory perception and discrimination of natural speech and computerized speech sounds from one another in children with ASD. Specifically, we compared a group of 4- to 6- year old high-functioning children with ASD with groups of typically developing (TD) children matched on gender, chronological age and verbal abilities. ERPs were recorded while children passively listened to pairs of stimuli that were either both natural speech sounds (match), both computerized speech sounds (match), speech followed by computerized speech (mismatch) or computerized speech followed by speech (mismatch). Both participant groups exhibited match/mismatch effects reflective of speech discrimination at approximately 330 to 350 ms post-stimulus (N330, P350). However, while the control groups exhibited N330 match/mismatch effects that were bilateral when a speech stimulus was followed by a computerized speech stimulus, this effect was only present in the left hemisphere for the participants with ASD. Furthermore, while the control groups exhibited match/mismatch effects at approximately 600 ms (central N600, temporal P600) when computerized speech was followed by a speech stimulus, these effects were absent in the ASD group. These findings suggest that children with ASD fail to activate right hemisphere mechanisms, likely associated with social or emotional aspects of speech perception, when distinguishing computerized speech from natural speech stimuli. Furthermore, the ASD participants failed to detect the change from computerized speech to speech at a late cognitive stage of evaluation. Together, these findings are consistent with the

hypothesis that children with ASD rely more distinctly on physical stimulus properties versus social or emotional cues when distinguishing speech sounds.

Introduction

Autistic spectrum disorder (ASD) is an umbrella term for neurodevelopmental disorders characterised by impairments in social interaction, communication, and restricted or repetitive interests and behaviours (American Psychiatric Association, 2013). ASD is a heterogeneous disorder —individual's degree of impairment varies widely in the core areas of language, cognition, and social-cognitive functioning. One striking feature of ASD is poor social orienting and joint attention skills (Dawson et al., 1998, Dawson et al., 2004). In addition, previous behavioural research has shown that, unlike typically developing children, children with autism do not demonstrate a preference for their mother's voice (Klin, 1991). This null preference was later replicated by Kuhl and colleagues, who used speech spoken by a woman who was not the child's mother compared with more closely matched non-speech stimuli (Kuhl et al., 2005). Along with other findings, these results have been presented as support for the hypothesis that failure to attend to social stimuli is an important aspect of the early development of autism, causally contributing to deficits in both social interaction and language skills (Dawson et al., 2004, Carver and Dawson, 2002, Dawson, Bernier, & Ring, 2012, see also McCleery et al., 2011).

In addition to evidence for reduced behavioral orienting to human voices, Kuhl and colleagues also found that variability in social orienting in the children with autism in their study was related to the children's speech discrimination skills. In order to investigate this, the children with ASD were first divided into two sub-groups based on whether or not they

exhibited a behavioural preference for speech versus non-speech stimuli. Next, their brain responses to phonetic changes in speech stimuli were recorded using an established ERP paradigm, the Mismatch Negativity (MMN). Results demonstrated that children with autism who exhibited a behavioural preference for non-speech over speech sounds failed to exhibit neural mismatch responses indicative of phonetic stimulus discrimination, whereas children with ASD who exhibited a behavioural preference for speech exhibited the same MMN responses as typically developing control children (Kuhl et al., 2005). The results of this study, therefore, demonstrated an association between behavioural orienting to speech stimuli and a neural marker for effective, automatic perceptual discrimination of phonetic aspects of speech stimuli in children with ASD.

In 2003, Ceponiene and colleagues utilised the MMN paradigm in order to examine the neural mechanisms of attentional orienting to both speech and non-speech stimulus changes in children with autism (Ceponiene et al., 2003). The results showed that while the control group exhibited expected attentional orienting responses at approximately 300 ms (P3a component activity) to rarely presented frequency contrast stimuli in all conditions, the children with autism failed to exhibit these (P3a, attentional orienting) responses during the speech contrast conditions (Ceponiene et al., 2003). These results further suggest that impairments in the neural systems that mediate involuntary orienting to changes in sounds may be relatively specific to the processing of speech stimuli in children with ASD.

In a more recent follow-up to Ceponiene and colleagues' study, Whitehouse and Bishop utilised a different variation of the MMN paradigm where they presented rare novel speech stimuli within a stream of repetitive non-speech stimuli and, separately, rare novel non-speech stimuli in the context of repetitive stream of speech stimuli (Whitehouse & Bishop, 2008). They found that the P3a responses were larger in children with autism relative

to controls in the repetitive non-speech condition (rare speech sound), whereas their P3a responses were smaller relative to controls in the repetitive speech condition (rare non-speech sound). These group differences, however, were not observed in an active condition in which children were required to pay attention to the sounds in order to perform a behavioural task. These results suggest that attentional orienting to, and detection of, speech sounds is not universally impaired in children with ASD. Instead, these results suggest that these children may "turn off" their discriminative and attentional orienting response systems when exposed to a repetitive stream of speech (Whitehouse & Bishop, 2008, see also McCleery et al., 2010).

The results of other studies suggest that autism may also be characterized by atypical lateralization of speech processing. For example, Seery and colleagues examined ERPs in response to both native and non-native speech sound discrimination in infants between 6 and 12 months of age at low risk (LR) and high-risk (HR) for developing ASD (Seery et al., 2012). The results showed that the neural discrimination of native and non-native speech sounds did not differ for the HR versus LR groups. However, while the LR group exhibited lateralized ERP responses to speech in a Late Slow Wave (LSW) component recorded from central electrode sites at both 9 and 12 months of age, the HR group failed to do so. This finding is consistent with the proposal that right-lateralized attentional brain networks involved in pre-attentive arousal processes are compromised in children with ASD (Stroganova et al., 2013). It is also consistent with the results of a recent MEG study that observed a reduction in right-lateralised auditory cortex responses to non-speech sounds, reflected in the amplitudes of P100m auditory component, in the ASD group relatively to controls. Additionally, a smaller amplitude P100m in the right hemisphere was associated with severity of sensory dysfunction in participants with ASD (Orekhova et al., 2012). On the other hand, a recent fMRI study (Redcay et al., 2008) of toddlers with ASD showed

atypically increased right hemisphere activation during the perception of speech. However, it is worth noting that Redcay and colleagues used semantically meaningful speech versus non-meaningful backward speech stimuli whereas simple non-speech stimuli and semantically meaningless speech stimuli (i.e., simple phonemes) were utilized in the abovementioned studies. Therefore, the differences in lateralization between Redcay and colleagues' fMRI study and previous findings might be explained by the cognitive semantic processing of speech stimuli.

Altogether, the evidence collected to date suggests a diminished response to speech stimuli compared with non-speech sounds, and atypical lateralization of neural responses to both speech and non-speech stimuli, in children with ASD. However, the mechanisms underlying the impairment of speech processing and detection in children with ASD remain largely unknown. Ceponiene and colleagues (Ceponiene et al., 2003) initially suggested that an impairment in the attentional orienting response specific to speech stimuli may lead to speech-specific perceptual and language dysfunction in ASD. On the other hand, Whitehouse and Bishop (2008) proposed that children with ASD "switch off" their orienting response for all types of novel sounds when presented with a stream of repetitive speech sounds. It is worth further noting that these two studies included ASD participants who had different language levels and abilities. Specifically, Ceponiene and colleagues utilized a sample with a mean chronological age of 8.9 and a mean verbal age of 3.4 years, while participants in Whitehouse and Bishop's study had a mean age of 10.4 and mean verbal age of 7.8 years. Additionally, in the Whitehouse and Bishop (2008) study, the speech and non-speech stimuli were not matched for frequency characteristics as they were in Ceponiene and colleagues' study. Therefore, differences in physical characteristics of the stimuli in the study may have contributed to the differences observed between speech and non-speech processing. Overall,

the results of the previous studies are not directly comparable and more studies needs to be carried out in order to identify the mechanisms underlying diminished responses to speech versus non-speech sounds in children with ASD.

One of the major limitations to the extant ERP literature examining speech versus non-speech processing is the heavy reliance on oddball paradigms. Specifically, the MMN paradigm utilized in all of the studies reviewed here relies on both habituation to a "standard" stimulus and dishabituation, reflected in a particular attentional orienting response (P3a), to a rarely presented "oddball" stimulus (see Kujala et al., 2013, for review). While the MMN paradigm is both well-established and powerful, there is good reason to believe that the neural responses produced by this paradigm do not directly reflect neural mechanisms associated with speech versus non-speech processing but, instead, are generated from a combination of perceptual and attentional networks (e.g., Doeller et al., 2003). Furthermore, there is specific evidence for atypicalities in both habituation (Guiraud et al., 2011) and attentional orienting networks (Stroganova et al., 2013) associated with autism spectrum disorders. Therefore, the almost exclusive reliance on the MMN in the autism speech and auditory processing literatures to date limits our current understanding of speech versus non-speech processing in this population.

In the current study we employ an auditory pair-repetition paradigm designed to allow for the direct and balanced assessment of the discrimination of speech and closely matched computerized speech (non-speech) stimuli from one another, without the recruitment of unrelated attentional orienting responses that may differ between the two groups. Similar immediate repetition/non-repetition design has been previously utilized in studies investigating discrimination of visual (facial) features (Rotshtein et al., 2005, 2007, Winston et al., 2004) and neural processing of visual and auditory action related stimuli (Giusti et al.,

2010, Pizzamiglio et al., 2005). In developmental population, several studies investigating neural mechanisms underlying speech and gesture perception have used similar pair match/mismatch ERP paradigms which are based on repetition of stimuli of the same or different perceptual categories (Dehaene-Lambertz & Baillet, 1998, Dehaene-Lambertz & Dehaene, 1994, Sheehan et al., 2007, McCleery et al., 2010). For example, Dehaene-Lambertz and Dehaene (1994) used an auditory repetition ERP paradigm and found syllable (/ba/ followed by /ga/) discrimination effects at a late stage of processing (400ms) over the frontal region in three-month-old infants. In another ERP study, toddlers watched a video-clip of gesture or a written word which was followed by a picture of an object which matched or did not match the video (Sheehan et al., 2007). The authors found the N400 congruency effects for both words and gestures in 18-month old toddlers, but only for words in 2-year old toddlers. Finally, McCleery and colleagues examined N400 responses to matched and mismatched auditory-visual pairs of stimuli in typically developing children and children with ASD (McCleery et al., 2010). The results showed that, unlike their typically developing peers, children with ASD did not elicit larger N400 response to congruent compared to incongruent word-picture stimuli (McCleery et al., 2010). However, to the best of our knowledge, an auditory pair-repetition paradigm has not been used before in studies of speech perception in children with ASD.

In the current study, we examine ERP responses to pairs of speech and computerized speech sounds, including a speech sound followed by another speech sound, a speech sound followed by another computerized speech sound, a speech sound followed by a computerized sound, and a computerized sound followed by a speech sound. The stimuli were phonetic sounds (/ba/, /da/, /ga/) and non-phonetic correlates of these speech sounds (/ba/, /da/, /ga/)

that were carefully matched to the speech sounds in regards to their physical characteristics. The results of a previous pilot study carried out on adult participants showed that adults were able to accurately distinguish these two categories of stimuli (speech, computerized speech) (Graham, 2014). The aim of this study was to examine the discrimination of speech and computerized speech from one another as perceptual categories of stimuli, through examining match and mismatch effects associated with these four types of stimulus pairings.

Based on previous findings, we predicted that between-group differences in the responses to speech and computerized speech sounds would be reflected in ERP components (e.g., 300 ms post-stimulus) associated with cognitive processing of speech which may reflect the recognition and classification of auditory stimuli (Lepisto et al., 2005, Lepisto et al., 2006; see also, O'Connor, 2012). We also predicted that control participants would exhibit mismatch effects both when speech followed computerized speech and when computerized speech followed speech, but ASD participants would fail to exhibit match/mismatch effects in one or both of these conditions. Finally, we predicted atypical lateralization of ERP responses to both speech and computerized speech sound processing in children with ASD. In order to focus our comparison on autism-related factors versus those associated with language dysfunction, we utilised a high-functioning, verbally competent sample of children with ASD. Finally, to further account for ERP effects that might be related to general biological and brain development factors versus verbal abilities, we utilised two control comparison groups which were matched with the ASD group on chronological age (CA) and verbal age (VA), respectively.

Methods

Participants

Fourteen children with high-functioning autism spectrum disorder (2 females, 12 males), and 16 typically developing children (2 females, 14 males), aged 4 to 6 years, as well as 3 typically developing younger children, aged 2 to 3 years (3 males), participated in the study. All ASD participants who were included in the final sample had a verbal age of more than 40 months. According to parent report, all TD and ASD participants learned English as a first language and did not have exposure to any other language (see questionnaires for parents, Apendices B). Sixteen TD participants were reported by their parents to be right handed, three were left-handed; eleven ASD participants were reported by their parents to be right handed and three left-handed. No child had a history of seizures or other medical or neurological disorder. All children had normal hearing and normal, or corrected to normal, vision. Nine ASD participants had an official diagnosis of an autism spectrum disorder by a licensed clinical psychologist or medical doctor not associated with this research, four other participants were either referred to a specialist or were in the process of obtaining a diagnosis. In all cases, a diagnosis of an Autism Spectrum Disorder was verified through the administration of Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord et al., 2000) in the laboratory by a formally trained researcher. In addition, the Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003) was used 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. No children in typically developing group received a score higher than 12, while all ASD children, but two, received a score of 16 or higher revealing autism symptomatology. The

SCQ scores in ASD children (M=22, S.E.=8.1) were significantly higher than scores in TD children (M=6.5, S.E.=3.4; MD=15.6, S.E.=2.3, $p<0.001$). Based on the results of the ADOS assessment and expert clinical judgement, all children in the ASD group met clinical diagnostic criteria for an Autistic Spectrum Disorder. Data from one additional child initially designated for the ASD group were excluded as he did not meet cut-off criteria for an Autism Spectrum Disorder on the ADOS.

The two comparison groups were matched on both chronological age (CA; 14 TD CA matched, 14 ASD children) and verbal age (VA; 14 TD VA matched, 14 ASD children; see **Table 5.1**). The behavioural measures employed for the assessment of verbal age of participants in both comparison groups included the Mullen Scales of Early Learning (MSEL, Mullen, 1995) or the British Ability Scales-II (BAS-II, Elliott, Smith & McCulloch, 1997), dependent upon the participant's age. Specifically, the MSEL was administered to 2- to 5-year old participants, whereas the BAS-II was utilised with 6-year old participants. Data from two more participants with ASD were excluded as their verbal age was observed to be less than 40 months. Finally, data from one additional participant in the ASD group and two children in the TD group were excluded due to prolonged exposure to a second language. In accordance with the ethics protocol approved by the University of Birmingham, parents of all children who took part in the study reviewed and signed an approved consent form for their child to participate.

Characteristics	ASD group (n=14)	TD CA group (n=14)	TD VA group (n=14)	Group comparison (p value)
Handedness	11 right, 3 left	11 right, 3 left	11 right, 2 left	N/A
Gender	12 male, 2 female	12 male, 2 female	12 male, 2 female	N/A
Chronological age in months (SD)	61 (8.8)	60 (10)	50 (11)	p=0.86 (ASD vs TD CA)
MSEL and BAS verbal age in months (SD)	55 (10)	63 (13)	55 (13)	p=0.82 (ASD vs TD VA)
MSEL and BAS non-verbal age in months (SD)	58 (10)	64(10)	56 (13)	p=0.12 (ASD vs TD V A); p=0.57 (ASD vs TD CA)
ADOS communication sub-scale	3.9 (1.2)	N/A	N/A	N/A
ADOS social interaction subscale	6.5 (1.9)	N/A	N/A	N/A
ADOS total score	10.5 (2.9)	N/A	N/A	N/A

Table 5.1. **Participants' characteristics**. Characteristics of children with ASD and typically developing (TD) children individually matched on chronological age (TD CA group) and verbal mental age (TD VA group) and the results of the group comparisons based on independent sample t-tests.

Stimuli

The stimuli were created by using the semi-synthetic speech generation method (SSG) and were previously utilized by Ceponiene and colleagues (Ceponiene et al., 2008). SSG method allows modifying natural speech according to the aims of the particular study. It was shown that by utilizing natural glottal excitation generated by the fluctuation of vocal folds, the periodic structure of the synthesised waveform can achieve a realistic prosody and jitter (Alku, Tiitinen & Näätänen, 1999).

Three consonant-vowel syllables, /ba/, /da/, and /ga/, spoken by a female English speaker, were recorded, digitized and used for computing the SSG in the current study. In particular, the glottal excitation waveform, the formant frequencies for the three consonants

(/b/, /d/, /g/), as well as formant frequencies for the vowel /a/ were processed. Additionally, a 30 ms pre-voice bar which is normally present in the /ba/ syllables, was added to the /da/ and /ga/ stimuli in order to make the same gross structure of stimuli. Following pre-constant voice bar, the consonant burst lasted for 10 ms. The consonant-to-vowel 80 ms transition was then followed by an identical steady-state vowel /a/ which lasted for 60 ms. In total, the duration of the syllable and non-phonetic correlate stimuli were 180 ms. The non-phonetic correlates of the three speech syllables were created from five sinusoidal tones. Specifically, the frequencies and intensities of the tones were computed by the SSG and were chosen on the basis of the syllable format frequencies. The spectra of burst and burst-to-steady state format transitions, duration and intensities of the non-phonetic stimuli were kept equal to those of the corresponding natural speech stimuli (Ceponiene, Torki, Alku, Koyama, & Townsend, 2008). As a result, synthesized stimuli were only different from corresponding speech stimuli in terms of their format transitions and plosives. The remaining acoustical features of the tones, including fundamental frequency, intonation and intensity duration were identical.

Procedure

In the current study, six different stimuli were used: three "speech" syllables (/ba/, /da/, and /ga/), and their three non-phonetic computerized speech "non-speech" correlates. In total, there were four experimental conditions: Speech Repeated (Speech Match), Speech Non-Repeated (Speech Mismatch), Non-Speech Repeated (Non-Speech Match), and Non-Speech Non-Repeated (Non-Speech Mismatch). Each trial consisted of two sounds which were presented with an inter-stimulus interval of 50 ms. The presentation of the second stimulus was followed by a longer inter-trial interval which varied between 475, 550 and 625

ms. The trials were pseudo-randomized and were presented using E-Prime 2.0 software (Psychology Software Tools). For each condition, an average of 430 trials was presented. After artefact detection, the following numbers of mean trials (standard error) per participant were produced for each condition: Speech Match: 206 (75) trials; Speech Mismatch: 202 (71) trials; Non-Speech Match: 219 (90) trials; Non-Speech Mismatch: 204 (74) trials. Each participant produced more than 50 viable trials per condition.

Speech and computerized stimuli were presented in a sound attenuated room via stereo speakers with a sound pressure level of 60 dB measured at the seated child's head. Children were seated in front of the computer screen that showed a silent cartoon video of their choice which was selected before the testing. The EEG recording and stimuli presentation lasted for approximately 30 minutes. Children were instructed to sit as still as possible while they were watching a silent video and the sounds were played in the background.

EEG Recording

EEG was recorded continuously using a 128-channel Hydrocel Geodesic Sensor Net (Electrical Geodesics, Eugene, Oregon) with a sample rate of 500 Hz, referenced to a vertex electrode Cz. Electrode impedances were kept below 100 KOm. EEG data were processed offline using Netstation 4.4.1 software (Electrical Geodesics, Eugene, Oregon). The data were filtered (bandpass filter = 0.1-40 Hz) and segmented to epochs starting 100 ms before and continuing 700 ms after the presentation of the first auditory stimulus in the trial. The EEG data trials were further processed using an artefact detection tool that marked channels bad if the max-min threshold exceeded 100 mV and marked trials bad if they contained more than

12 bad channels. Individual electrodes were marked bad if they contained artefacts for more than 20% of recording. Following this automated procedure, remaining trials were also visually inspected by a trained observer and excluded from the analysis if they contained more than 12 bad channels, eye blinks and/or eye movements. Following artefact correction procedure, bad channels in the EEG data were replaced using a spherical spline interpolation algorithm (Srinivasan, et al., 1996). The data were then averaged, re-referenced to an average reference for each participant and baseline corrected to a 100 ms pre-stimulus interval.

ERR components

The ERP components in the central and frontal areas were as follows: positive going component peaking at 140 ms (P100), negative going component peaking at approximately 280 ms (N250), positive going component peaking at 350 ms (P350) and negative going Late Slow Wave (LSW) peaking at 600 ms (N600). In the temporal area, the ERP components were the following: negative going component peaking at 150 ms (N100), positive going component peaking at 280 ms (P250), negative going component peaking at 330 ms (N330), finally positive going LSW peaking at 600 ms (P600).

Electrode locations included in the analysis were determined by visual inspection of individual data as well as grand average data of 14 participants with ASD, 14 control participants matched on verbal age (TD VA) and 14 control participants matched on chronological age (TD CA). Based on our predictions and careful visual inspection of the data as well as on the previous ERP findings of speech processing in ASD (Kuhl et al., 2005, Ceponiene et al., 2003, Whitehouse & Bishop, 2008), 14 frontal (7 left hemisphere, 7 right hemisphere), 14 central (7 left hemisphere, 7 right hemisphere) and 12 temporal (6 left

hemisphere, 6 right hemisphere) electrodes were identified for the analysis (see **Figure 5.1**). Peak amplitudes and latencies-to-peak amplitudes were analysed for all components except for the Late Slow Wave component, for which mean amplitudes were analysed. Time windows were selected for each component on the basis that the window encompassed the peak of the grand average for each condition, and also accurately measured the peak of the component for each condition for each individual participant.

The following time windows were selected for each component in the frontal and the central areas: 110-190 ms (P100), 230-320 ms (N250), 300 – 420 ms (P350), 500-700 ms (N600). In addition, the following time windows were selected for each component in the temporal area: 100-200 ms (N100), 230-320 ms (P250), 300-430 ms (N330) and 500-700 ms (P600).

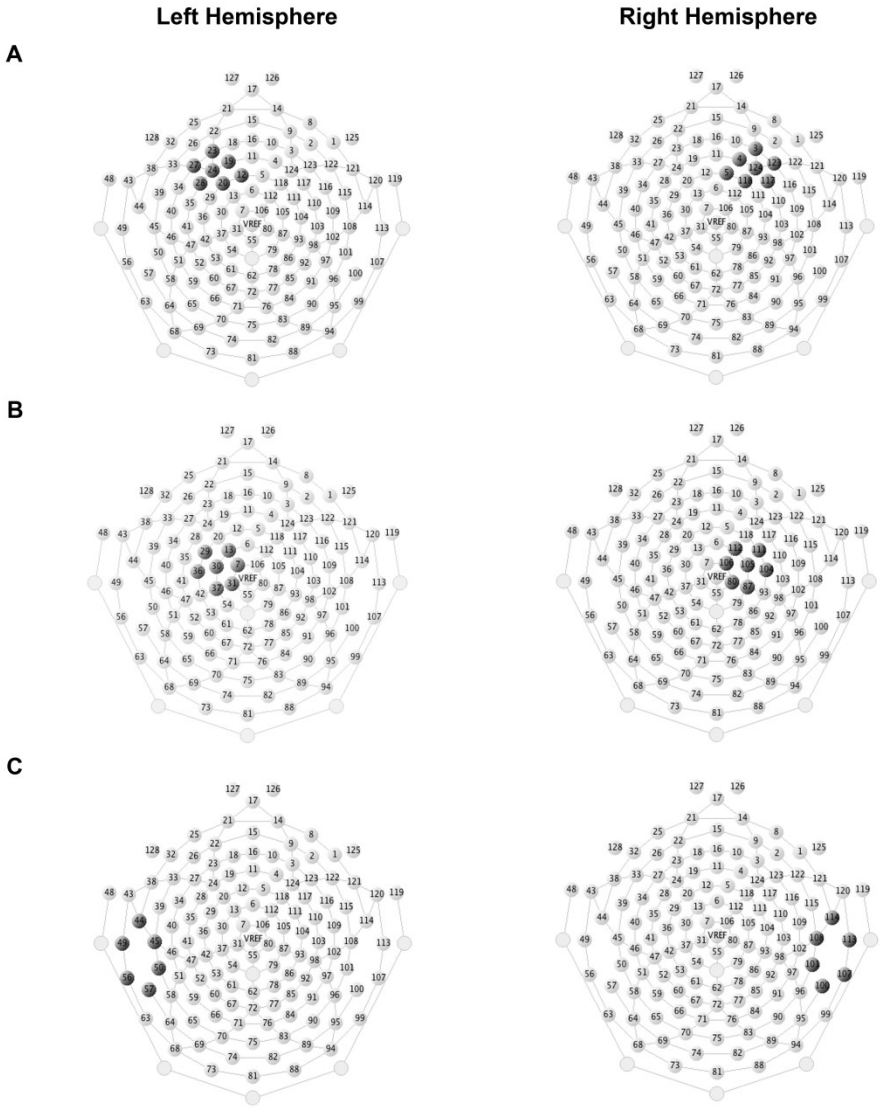


Figure 5.1. Location of the electrodes. Electrodes selected for the analysis in the frontal (A), central (B) and temporal (C) areas.

A repeated-measures ANOVA with Hemisphere (Left vs Right), Stimulus (Speech vs Non-speech) and Repetition (Repeated vs Non-Repeated) as within-subject factors and Group (ASD vs TD) as a between-subject factor was performed on the peak (P100, N100, N250, N330, P250, P350) and mean (N600, P600) amplitudes and latencies of the abovementioned components in the frontal, central and temporal areas separately. Post-hoc paired sample t-tests were run to explore further significant interactions that included factors of Stimulus, Repetition and Group, or Repetition and Group. Bonferroni corrections were employed for all

post-hoc paired sample comparisons. The results that reached the significant level ($p<0.05$) or tendency ($p<0.1$) in comparisons between ASD vs TD VA matched groups as well as ASD vs TD CA matched groups are reported below. However, only the results that showed significant effects in both TD VA and TD CA comparison groups are further addressed in the discussion. The ERP waveforms for the ASD versus TD VA group, and the ASD vs TD CA comparison group in the central and temporal areas are presented in **Figure 5.2** and **Figure 5.3**, respectively.

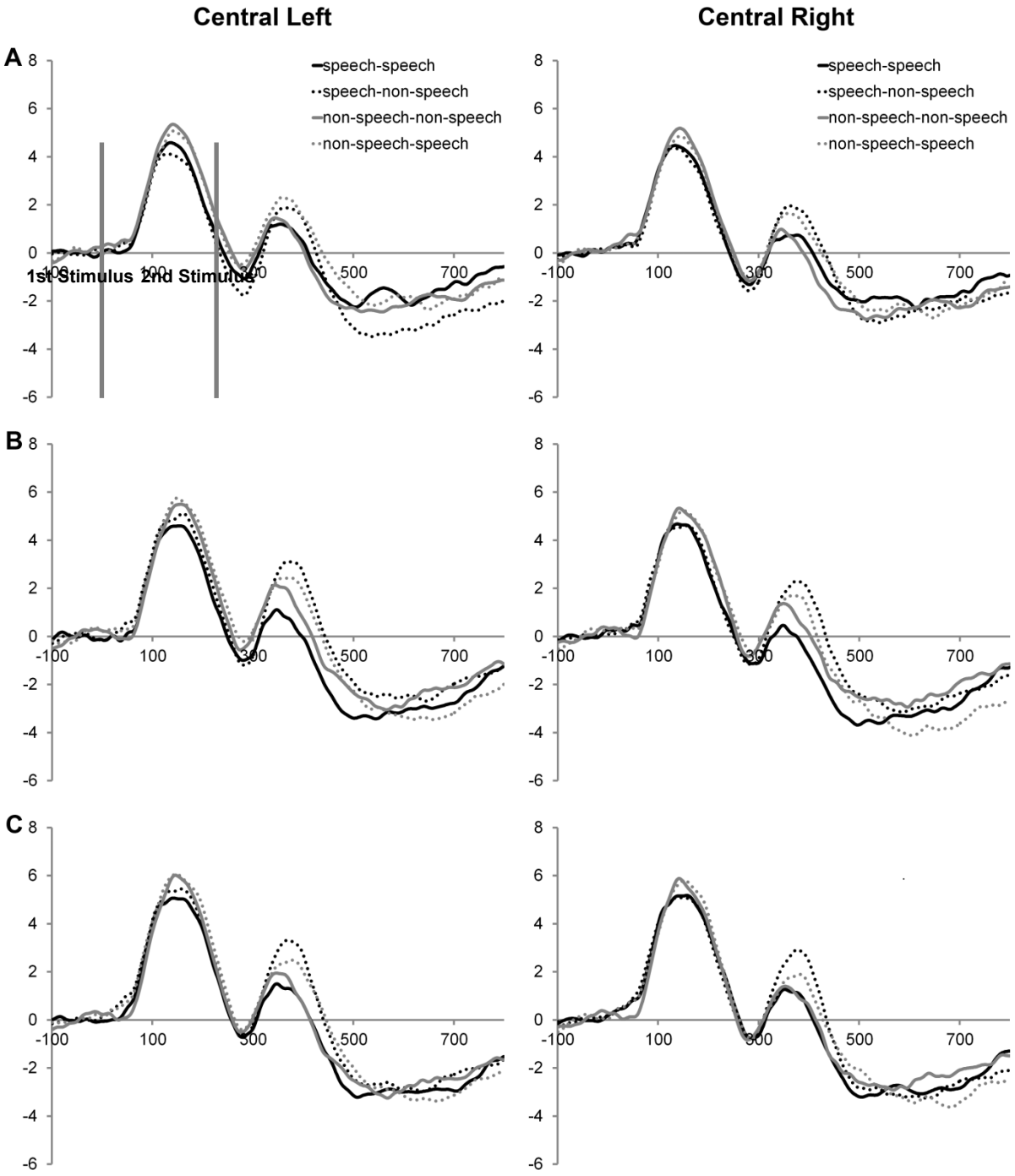


Figure 5.2. ERP waveforms in the central area. The figure represents the ERP waveforms recorded over the central left (left side) and central right (right side) electrodes in the ASD (A) and TD control groups matched on verbal (TD VA) (B) and chronological age (TD CA) (C).

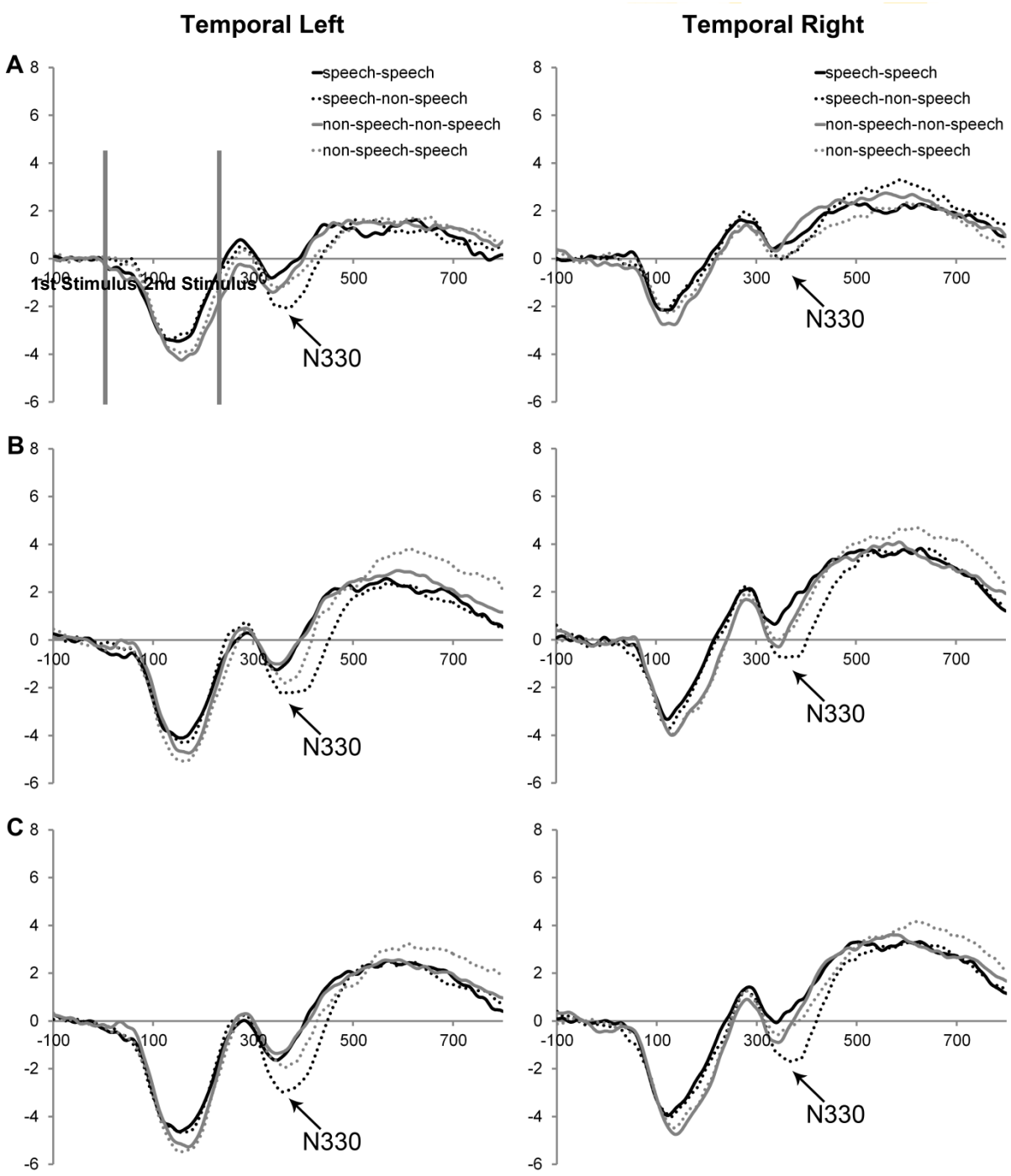


Figure 5.3. **ERP waveforms in the temporal area.** The figure represents the ERP waveforms recorded over the temporal left (left side) and temporal right (right side) electrodes in the ASD (A) and TD control groups matched on verbal (TD VA) (B) and chronological age (TD CA) (C).

Results

ERP effects –ASD vs TD VA matched group

Frontal and Central Components

Early (sensory-perceptual) components (P100 and N250)

A repeated-measures ANOVA with within-subject factors of Hemisphere (Left vs Right), Stimulus (Speech vs Non-speech), Repetition (Repeated vs Non-Repeated) and a between-subject factor of Group (ASD vs TD VA) carried out on the P100 latency over the frontal and central areas revealed a main effect of Stimulus in the both areas ($F(1;26)=8.7$, $p<0.01$; $F(1;26)=9.4$, $p<0.01$). The same results were obtained from the analysis on the P100 amplitude over the central region ($F(1;26)=16.2$, $p<0.001$). Additionally, for the latency of N250 component in the frontal area, there was a main effect of Stimulus ($F(1;26)=29$, $p<0.001$), main effect of Hemisphere ($F(1;26)=8$, $p<0.01$) and significant interaction between Hemisphere and Group ($F(1;26)=4.2$, $p=0.05$). No significant effects were found for the amplitude of the N250 component in the both areas.

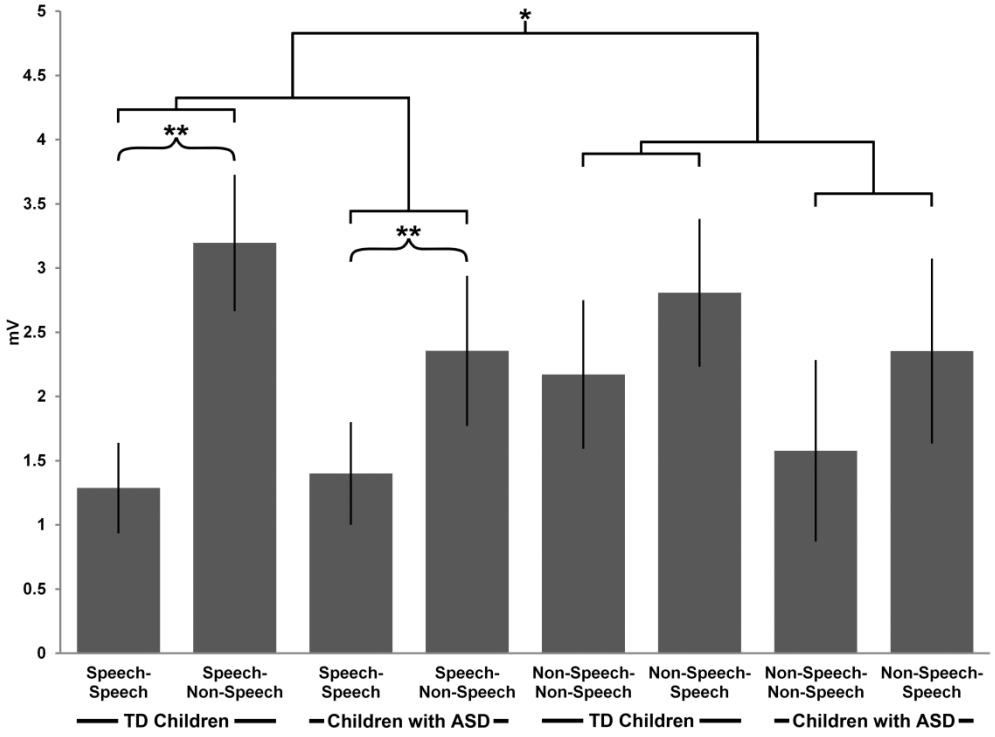
Late (cognitive) components (P350, N600)

A repeated measures ANOVA with within-subject factors of Hemisphere (Left vs Right), Stimulus (Speech vs Non-speech), Repetition (Repeated vs Non-Repeated) and a between-subject factor of Group (ASD vs TD VA) revealed a main effect of Repetition for the amplitude of P350 component ($F(1;26)=36$, $p<0.001$; $F(1;26)=27$, $p<0.001$) in the frontal and the central areas, a significant interaction between Stimulus and Repetition ($F(1;26)=9.5$, $p<0.01$) in the both areas, as well as a significant interaction between Stimulus, Repetition

and Group ($F(1;26)=5.2$, $p<0.05$) in the central area. The post-hoc comparisons for the latter interaction showed a difference in processing match versus mismatch speech sounds, with a higher amplitude to mismatch sounds (mismatch effect) in the condition, in which a speech stimulus was followed by a non-speech stimulus in both the TD (MD=-1.7, S.E.=0.4, $p<0.01$) and the ASD groups (MD=-1, S.E.=0.4, $p=0.01$) (see **Figure 5.4a**). Additionally, for the latency of the P350 component, there was a significant main effect of Repetition in the both areas ($F(1;26)=32.3$, $p<0.001$; $F(1;26)=26.7$, $p<0.001$), as well as a main effect of Stimulus in the frontal area ($F(1;26)=8.7$, $p<0.01$).

There was also a main effect of Repetition ($F(1;26)=7$, $p=0.01$) and significant interactions between Stimulus, Hemisphere and Group ($F(1;26)=4.9$, $p<0.05$) and between Stimulus, Repetition and Group ($F(1;26)=6.5$, $p=0.02$) revealed for the amplitude of the N600 component in the central area. Follow-up t-tests for the latter interaction indicated a significant mismatch effect, i.e higher ERP amplitude to mismatch sounds, in the condition where a non-speech sound was followed by a speech sound in the TD group (MD=-1.2, S.E.=0.4, $p<0.01$), while the ASD showed a mismatch effect in the condition in which speech was followed by non-speech (MD=-0.9, S.E.=0.3, $p<0.05$) (see **Figure 5.5a**). The post-hoc paired sample t-tests for the interaction between Repetition, Hemisphere and Group showed a tendency for the between group lateralization differences for processing match and mismatch sounds. In particular, mismatch sounds exhibited a higher ERP amplitude, compared to match sounds in the right hemisphere (MD=0.9, S.E. =0.5, $p=0.1$), while the ASD group exhibited the mismatch effect in the left hemisphere (MD=0.8, S.E.=0.4, $p=0.1$) (see **Figure 5.7a**).

5.4 A



5.4 B

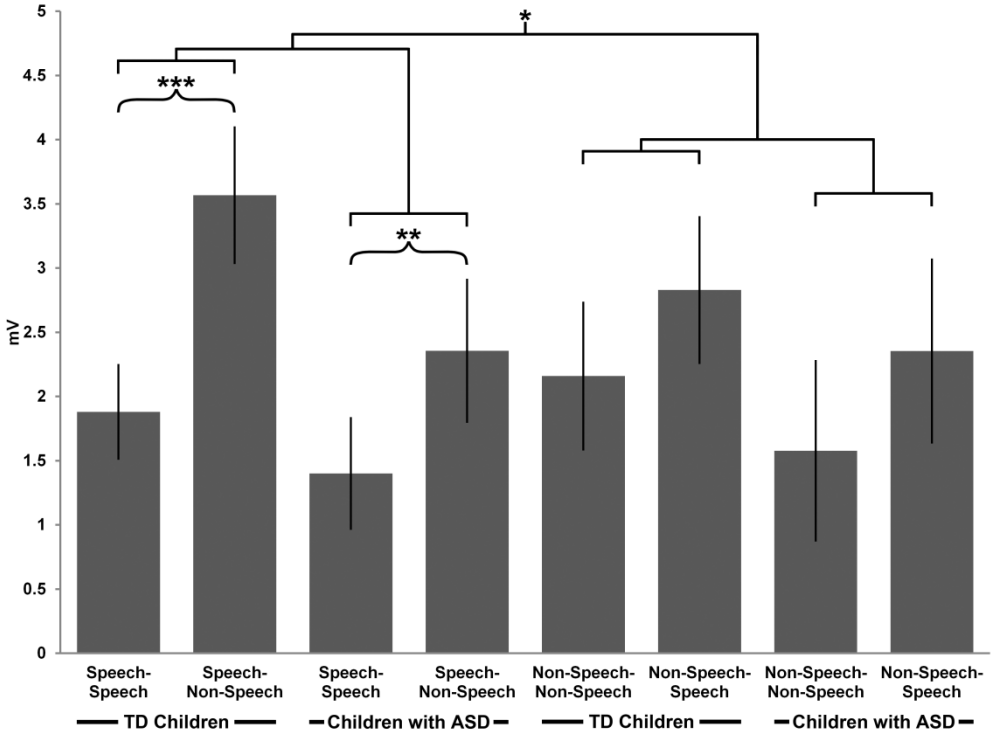
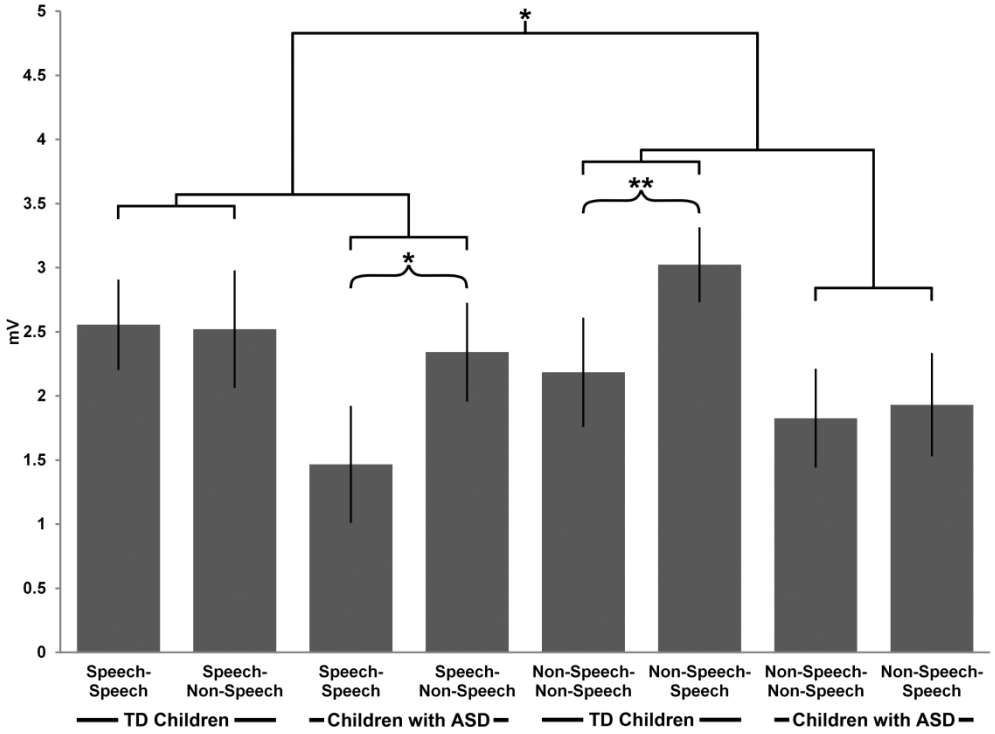


Figure 5.4. The P350 mismatch effect. The bar graph represents the mean ERP amplitudes for the P350 component in the central area in the four experimental conditions in the ASD and TD VA groups (A); in the ASD and TD CA groups (B). *** - $p<0.001$, ** - $p<0.01$, * - $p<0.05$.

5.5 A



5.5 B

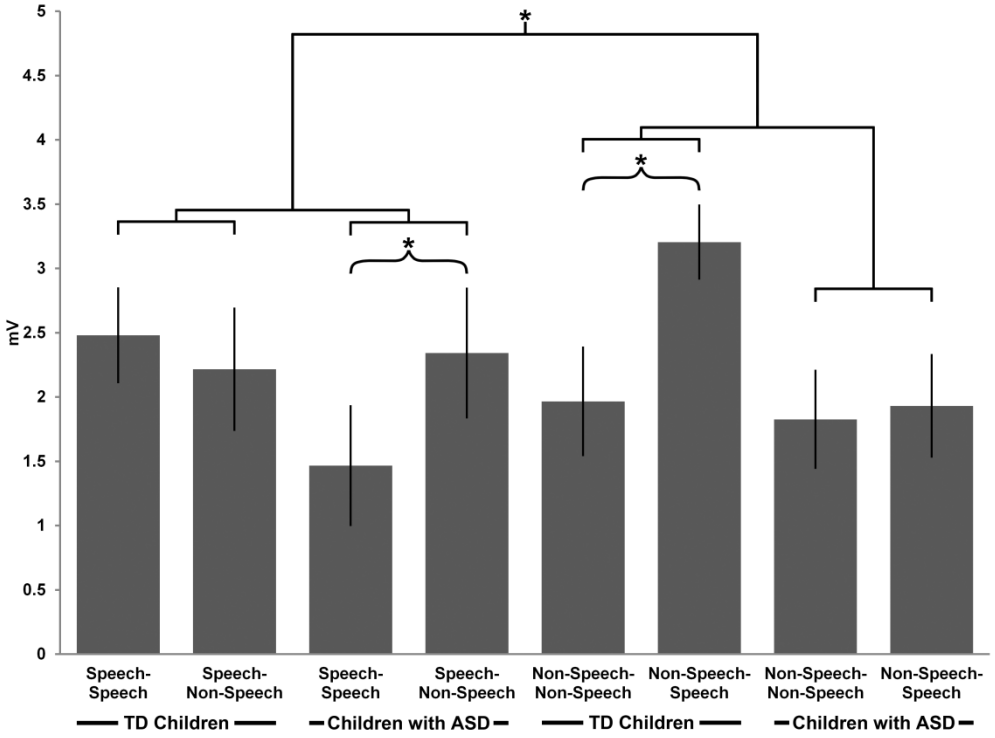


Figure 5.5. The N600 mismatch effect. The bar graph shows the mean ERP amplitudes for the N600 Late Slow Wave component in the central area in the four experimental conditions in the ASD and TD VA groups (A); in the ASD and TD CA groups (B). ** - $p<0.01$, * - $p<0.05$.

Temporal Components

Early (sensory-perceptual) components (N100 and P250)

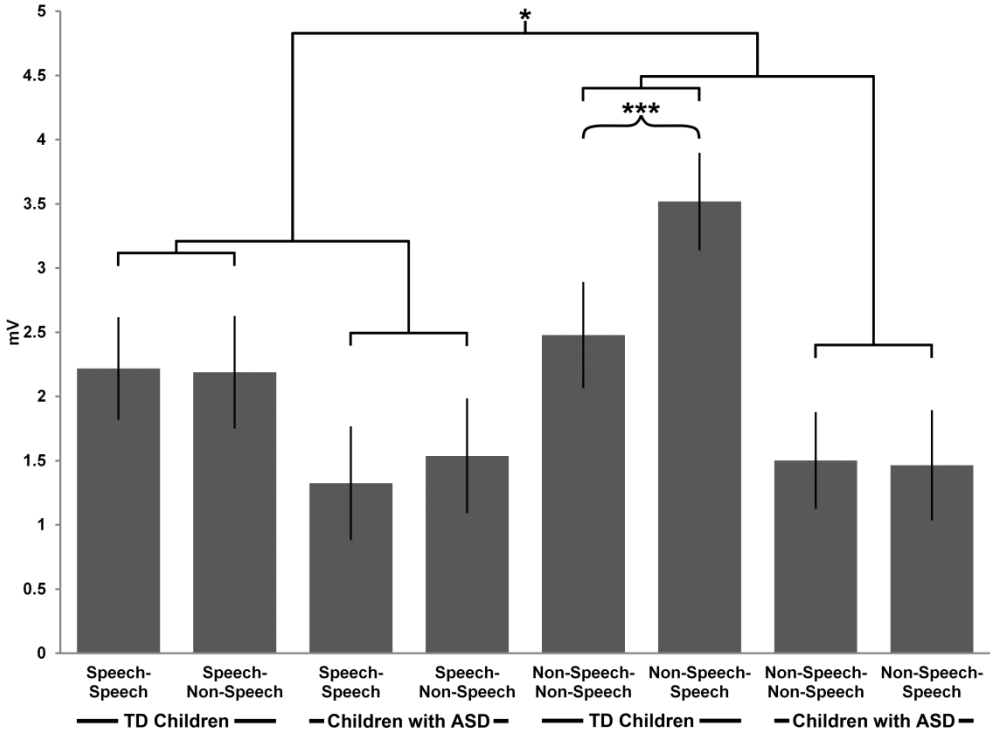
A repeated measures ANOVA with within-subject factors of Hemisphere (Left vs Right), Stimulus (Speech vs Non-speech), Repetition (Repeated vs Non-Repeated) and a between-subject factor of Group (ASD vs TD) carried on the amplitude and the latency of the N100 component revealed a main effect of Stimulus ($F(1;26)=25.7$, $p<0.001$; $F(1;26)=42.7$, $p<0.001$) as well as a main effect of Hemisphere ($F(1;26)=21$, $p<0.001$). No effects were revealed for the amplitude and the latency of the P250 component.

Late (cognitive) components (N330 and P600)

A repeated measures ANOVA carried on the amplitude of the N330 component revealed a main effect of Repetition ($F(1;26)=21.3$, $p<0.001$), a significant interaction between Stimulus and Repetition ($F(1;26)=8.8$, $p<0.01$) and a significant interaction between Stimulus, Repetition, Hemisphere and Group ($F(1;26)=5$, $p<0.05$).The post-hoc paired sample t-tests showed between-group lateralization differences for a mismatch effect, in the condition where a speech stimulus was followed by a non-speech stimulus. In particular, for the N330 component, the speech mismatch effect was present in the both hemispheres in the TD group (MD=1.3, S.E.=0.3, p=0.001; MD= 1.6, S.E. =0.5, $p<0.01$), while the ASD group exhibited the same effect in the left hemisphere only (MD=1.2, S.E.=0.3, p=0.001) (see **Figure 5.3**). For the latency of the N330 component, there was a significant main effect of Stimulus ($F(1;26)=6.5$, $p<0.05$) as well as a main effect of Repetition ($F(1;26)=66.5$, $p<0.001$). For the amplitude of the P600 component, a main effect of Stimulus ($F(1;26)=4$, $p=0.05$) and a

significant interaction between Stimulus, Repetition and Group ($F(1;26)=6.1$, $p<0.05$) as well as the between-subject factor of Group were revealed ($p<0.05$). The significant interaction between Stimulus, Repetition and Group indicated a mismatch effect in the condition where non-speech was followed by speech in the TD group (MD=1, S.E.=0.3, $p<0.001$), while the ASD group did not exhibit any differences ($p>0.1$) (see **Figure 5.6a**). Finally, a between subject factor of Group indicated less the P600 component activity in the ASD group compared to the TD group ($p<0.05$).

5.6 A



5.6 B

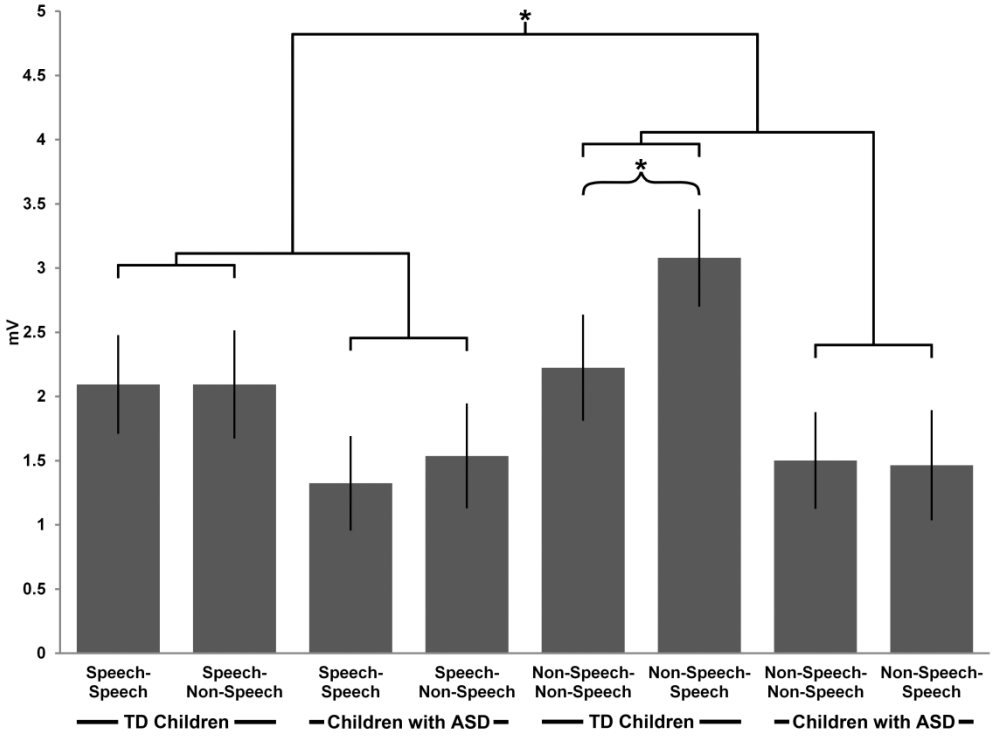


Figure 5.6. The P600 mismatch effect. The bar graph shows the mean ERP amplitudes for the P600 Late Slow Wave component in the temporal area in the four experimental conditions in the ASD and TD VA groups (A); the ASD and TD CA groups (B). *** - $p<0.001$, ** - $p<0.01$, * - $p<0.05$.

ERP effects – ASD vs TD CA matched group

Frontal and Central components

Early (perceptual) components (P100 and N250)

A repeated measures ANOVA with within-subject factors of Hemisphere (Left vs Right), Stimulus (Speech vs Non-speech), Repetition (Repeated vs Non-Repeated) and a between-subject factor of Group (ASD vs TD CA) revealed a main effect of Speech for the latency of P100 component in the frontal ($F(1;26)=8$, $p<0.001$) and the central areas ($F(1;26)=14$, $p=0.001$). The main effect of Stimulus was also revealed for the amplitude of the P100 component in the both areas ($F(1;26)=4.4$, $p=0.01$; $F(1;26)=16$, $p<0.001$). For the latency of the N250 component in the frontal area, there were the following effects: a main effect of Stimulus ($F(1;26)=21.7$, $p<0.001$), a main effect of Repetition ($F(1;26)=4.4$, $p<0.05$) as well as a main effect of Hemisphere ($F(1;26)=6.7$, $p<0.05$). No further significant effects were revealed for the latency and the amplitude of the N250 component.

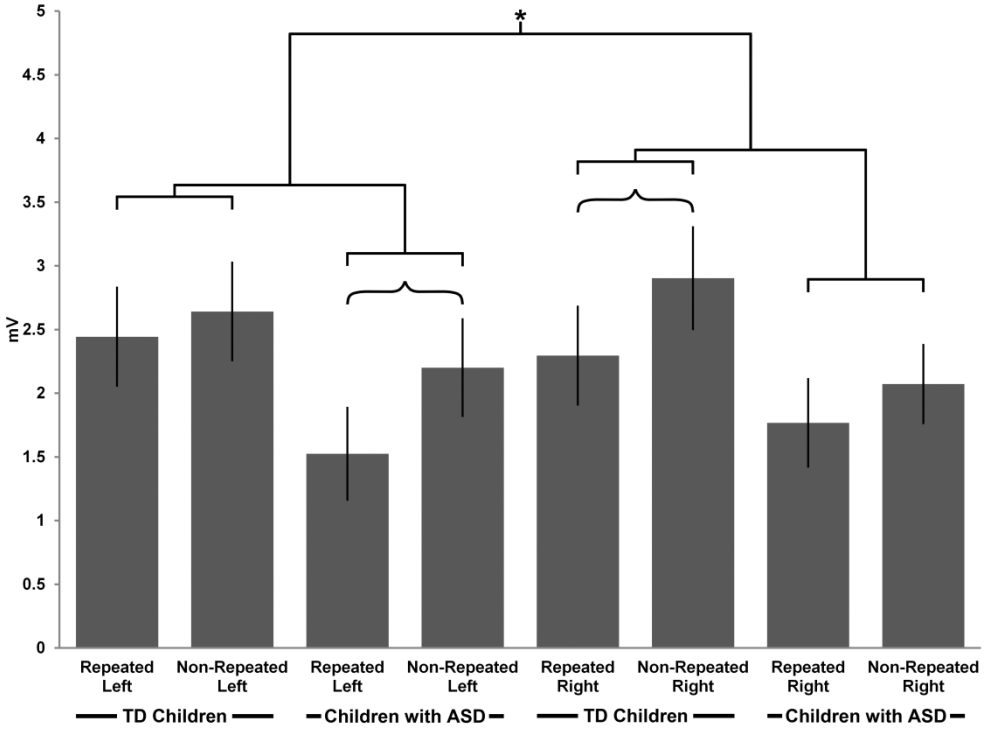
Late (cognitive) components (P350 and N600)

A repeated measures ANOVA carried on the amplitude of the P350 component revealed a main effect of Repetition ($F(1;26)=23.6$, $p<0.001$; $F(1;26)=18$, $p<0.001$), a significant interaction between Stimulus and Repetition ($F(1;26)=7.2$, $p<0.01$; $F(1;26)=9.9$, $p<0.01$) in the both areas as well as a main effect of Stimulus in the frontal area ($F(1;26)=4.5$, $p<0.05$). Additionally, an interaction between Stimulus, Repetition and Group was marginally significant ($F(1;26)=3.5$, $p=0.07$). Follow-up paired sample t-tests for the latter interaction revealed a mismatch effect in the speech mismatch condition in both the TD (MD=-1.7,

S.E.=0.4, p<0.001) and the ASD groups (MD=-1, S.E.=0.4, p=0.01) (see **Figure 5.4b**). For the latency of the P350 component, there was a main effect of Stimulus (F(1;26)=8.5, p<0.01; F(1;26)=7, p=0.01) and a main effect of Repetition (F(1;26)=46, p<0.001; F(1;26)=30.8, p<0.001) in the both areas.

For the amplitude of the N600 component in the central area, a main effect of Repetition (F(1;26)=7, p=0.01), a significant interaction between Stimulus, Repetition and Group (F(1;26)=4.9, p<0.05) and a significant interaction between Repetition, Hemisphere and Group (F(1;26)=4.5, p<0.05) were revealed. Follow-up t-tests for the latter interaction revealed a significant mismatch effect, indicated by a higher amplitude to mismatch compared with match sounds, in the right hemisphere in the TD group (MD=0.6, S.E.=0.3, p<0.05), while this difference was present in the left hemisphere in the ASD group (MD=0.7, S.E.=0.3, p<0.05) (see **Figure 5.7b**). The follow-up t-tests for the interaction between Stimulus, Repetition and Group showed a significant mismatch effect in the condition in which non-speech was followed by speech in the TD group (MD=0.8, S.E.=0.4, p=0.05). On the contrary, the ASD group exhibited a significant mismatch effect in the condition where a speech sound was followed by a non-speech sound (MD=0.9, S.E.=0.3, p<0.05) (see **Figure 5.5b**).

5.7 A



5.7 B

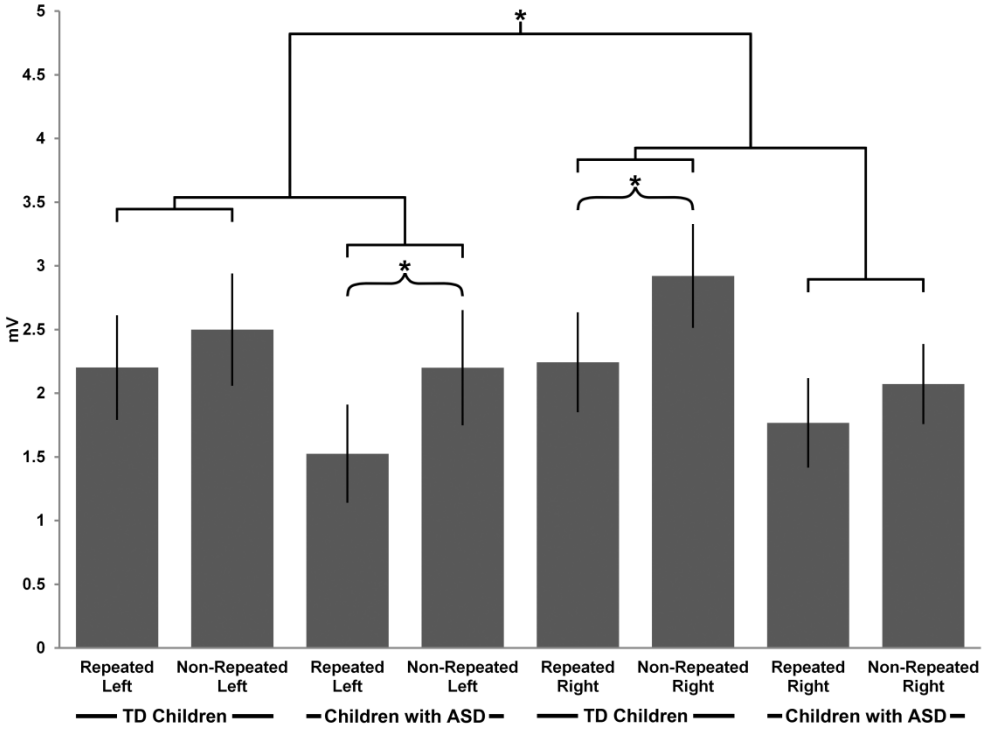


Figure 5.7. Lateralization effect in the central area. The bar graph shows the lateralization mismatch effect for the N600 Late Slow Wave component in the central area in the ASD and TD VA groups (A); the ASD and TD CA groups (B). * - $p<0.05$, bracket with no anterisk - $p=0.1$

Temporal Components

Early (perceptual) components (N100 and P250)

ANOVA with within-subject factors of Hemisphere (Left vs Right), Speech (Speech vs Non-speech), Repetition (Repeated vs Non-Repeated) and a between-subject factor of Group (ASD vs TD) revealed a main effect of Speech $F(1;26)=24.7$, $p<0.001$; $F(1;26)=36.7$, $p<0.001$) as well as a main effect of Hemisphere ($F(1;26)=22$, $p<0.001$) for the amplitude and the latency of the N100 component. No effects were found for the amplitude and the latency of the P250 component.

Late (cognitive) components (N330 and P600)

A repeated measures ANOVA carried on the amplitude of N330 component revealed a main effect of Repetition ($F(1;26)=29.5$, $p<0.001$), a significant effect of Hemisphere ($F(1;26)=11.2$, $p<0.01$), a significant interaction between Stimulus and Repetition ($F(1;26)=12.5$, $p<0.01$), as well as a significant interaction between Stimulus, Repetition, Hemisphere and Group ($F(1;26)=6.6$, $p=0.02$). The follow-up t-tests for the latter interaction showed a significant mismatch effect in the condition in which a speech sound was followed by a non-speech sound, over the both hemispheres in the TD group (MD=1.3, S.E.=0.3, $p<0.001$, MD=1.6, S.E.=0.4, $p<0.001$), while the ASD group exhibited the same effect in the left hemisphere only (MD=1.2, S.E.=0.3, $p=0.01$) (see the ERP waveforms in **Figure 5.3**). For the latency of N330 component, a main effect of Repetition ($F(1;26)=58$, $p<0.001$) was found. Finally, for the amplitude of P600 component, the following effects were revealed: a main effect of Stimulus ($F(1;26)=3.5$, $p<0.001$), a main effect of Hemisphere ($F(1;26)=12.6$,

p<0.01) as well as a marginally significant interaction between Stimulus, Repetition and Group (F(1;26)=3.7, p=0.07). The follow-up t-tests for this interaction showed that the latter interaction was driven by the ERP amplitude difference between mismatch and match non-speech sounds, with a higher amplitude to mismatch sounds, in the condition where a non-speech stimulus was followed by a speech stimulus in the TD group (MD= 0.9, S.E.=0.3, p<0.05), whereas the ASD group did not exhibit any significant differences (p>0.1) (see **Figure 5.6b**). Finally, there was a tendency for a between-subject factor of Group which indicated less the P600 component activity in the ASD group, relative to the controls (F(1;26)=3.7, p=0.06).

Discussion

In the current study, we investigated the ERP responses to speech and computerized speech sounds using a pair-repetition paradigm. To our best knowledge, this is the first ERP study to investigate the perception of speech and computerized speech in children with ASD without the impact of oddball stimuli and associated attentional orienting responses (see e.g., Ceponiene et al., 2003, Lepisto et al., 2005, Lepisto et al., 2006; see also Doeller et al., 2003). The current data revealed that the speech mismatch effects at the N330 temporal and the P350 central components, which were indicated by higher ERP amplitudes to mismatch sounds in the condition where speech was followed by computerized speech, were present in both the ASD and TD groups. Additionally, these results demonstrated the between-group differences in the lateralization of the speech mismatch effect revealed at the N330 component. Specifically, the N330 mismatch effect was present in the both right and left temporal regions in the TD group, while the ASD group exhibited the same effect over the left temporal region

only. Finally, the between-group differences in the presence or absence of speech/non-speech mismatch effects were identified for the late cognitive, the P600 temporal and the N600 central components. In particular, in the TD group, the non-speech mismatch effects at the both components were exhibited in the condition where computerized speech was followed by speech. On the contrary, these mismatch effects were absent in the ASD group at the both components, but present at the N600 component in the condition where speech was followed by a computerized speech stimulus. Overall, the current findings are consistent with the previous research suggesting that the between-group differences in speech versus non-speech processing mechanisms are associated with the late cognitive ERP component differences (after 300 ms) in the temporal and central areas (Kuhl et al., 2005, Lepisto et al., 2005, Lepisto et al., 2006, Lepisto et al., 2007). Additionally, the current findings suggest that the specific speech processing abnormalities in ASD might be characterized by atypical lateralization of the speech mismatch effect at approximately 330 ms, as well as an absence of the non-speech mismatch effects at the late cognitive stages of processing at 600 ms, reflecting categorization of speech preceded by a computerized speech stimulus.

A particular strength of the present study is the use of the two control comparison groups matched on the chronological and verbal mental age. More specifically, children in TD CA and TD VA groups were matched one by one on chronological and verbal mental age, respectively, with the ASD group. By considering the results that were consistent between comparisons with both of these two comparison groups, we ensured that the current findings are not influenced by the between-group differences in general biological and brain development or by language abilities. Furthermore, we used phonetically simple speech stimuli, which do not elicit semantic processing mechanisms. Finally, since the speech and non-speech stimuli were closely matched on frequency and other critical physical

characteristics, we significantly reduced the possibility that uncontrolled differences in the physical characteristics of the stimuli may have impacted upon group differences in speech discrimination in the current study. It is worth noting that the current findings identified the between-group differences associated with speech versus computerized speech processing over central and temporal regions, even though these effects did not reach significance level in the frontal area. However, it might be possible that our choice of electrodes included some fronto-central electrodes in the central montage (see **Figure 5.1**). Therefore, the current results are consistent with the previous research which revealed the ERP component differences associated with speech processing in the frontal-central and temporal regions (Kuhl et al., 2005, Lepisto et al., 2005, Lepisto et al., 2006, Whitehouse & Bishop, 2008).

One interesting finding was revealed for the amplitudes of the P350 central and the N330 temporal components. Both components exhibited a mismatch effect in the both TD and ASD groups, in the condition where a speech stimulus was followed by a computerized speech stimulus. This finding of the intact speech mismatch effect in the ASD group allows us to suggest that children with autism can discriminate non-speech sounds if preceded by speech. This is consistent with the previous findings showing that children with ASD can attend to and detect the acoustic changes in non-speech sounds, which exhibits the same or enhanced ERP responses, relative to controls (Lepisto et al., 2005, Lepisto et al., 2006; for a review, see Kujala et al., 2013). On the other hand, the current findings seem to contradict the previous findings of Whitehouse and Bishop's study suggesting that children with ASD do not respond to a non-speech sound presented in the stream of speech sounds (Whitehouse & Bishop, 2008). It is worth noting though that Whitehouse and Bishop concluded that children with ASD can voluntarily inhibit their responses to a *repetitive* stream of speech, but not a repetitive stream of non-speech sounds (Whitehouse and Bishop, 2008). Additionally, the

speech and non-speech stimuli utilized in their study were not matched on frequency characteristics, as they were in the current study. Therefore, one can suggest that it is the differences in the experimental design and the nature of the stimuli used in the current and Whitehouse and Bishop's studies that determine the differences in the ERP responses to speech and non-speech stimuli between the two studies.

In addition to the P350 and the N330 mismatch effects, the present data revealed the speech/non-speech mismatch effects for the late slow wave (LSW) ERP components: the N600 and the P600 components in the central and the temporal area, respectively. More specifically, as mentioned earlier, these effects were indicated by higher ERP amplitudes to mismatch compared to match sounds at the both components, in the condition where computerized speech was followed by a speech sound, in the TD group. On the contrary, the ASD group exhibited a mismatch effect at the N600 component, in the condition where speech was followed by a computerized sound. Taken together, these findings suggest that in the situation where a computerized stimulus is presented first, the ASD group exhibits a reduced cognitive evaluation of the fact that a subsequent speech sound is different from the preceding non-speech sound. This finding is again consistent with existing literature that has suggested a deficient involuntary orienting to speech and processing of speech sounds in children with autism (Ceponiene et al., 2003, Kuhl et al., 2005, Lepisto et al., 2005, Lepisto et al., 2006, Whitehouse & Bishop, 2008). Additionally, the current results extend the previous findings suggesting that specific speech processing abnormalities in ASD might be associated with a lack of detection and evaluation of speech as being different from preceding non-speech that occurs at the late cognitive stages.

It is worth noting that the ERP differences representing speech/non-speech mismatch effects were absent for the early sensory-perceptual ERP components (N100, P200, N200)

before 300 ms. As described above, the speech/non-speech mismatch effects were only identified in the amplitudes of later cognitive components (after 300 ms) in the temporal and central regions, and were either present in both groups (N330, P350), or present in one of the groups (P600, N600). Together, the timings of the revealed mismatch effects suggest that these effects were driven by an early cognitive processing of stimuli, such as detection and discrimination of the two stimuli (N330, P350), followed by a later cognitive evaluation of speech and computerized speech stimuli (N600, P600), occurring in the central and temporal regions. Thus one possible interpretation of the presence of the speech mismatch effects at the N330, the P350 and the N600 components, and the absence of the non-speech mismatch effects at the N600 and the P600 components in children with autism is that the order of the sounds presentation matters for their ability to discriminate sounds. More specifically, children with ASD are able to identify and process a *non-speech* sound preceded by a speech sound at approximately 330 ms to 350 ms and 600 ms, but fail to distinguish a *speech* sound from a preceding non-speech sound during the late cognitive evaluation stage at 600 ms.

Along with diminished detection of speech sounds, children with ASD also exhibited atypical lateralization revealed at the N330 temporal and the N600 central components. At the N330 temporal component, the TD group exhibited a bilateral mismatch effect in the condition where speech was followed by a computerized sound, while the ASD group demonstrated a *left* lateralized mismatch effect in the same condition. Additionally, at the P600 central component, the TD group exhibited an overall mismatch effect, reflected in the significant interaction between Repetition, Hemisphere and Group in the right hemisphere. On the contrary, the ASD group demonstrated the same effect in the mismatch conditions, which was lateralized to the left hemisphere. Taken together, the current findings suggest that, independently of the stimuli category, children with ASD exhibit a leftward

lateralization in processing auditory sounds, which might be driven by atypical processing of both sounds in the temporal and central regions.

This finding of the leftward lateralization of the mismatch effects at the N330 and the N600 components in the ASD group is consistent with the previous EEG and fMRI research which showed an atypical leftward lateralization in processing auditory sounds, including speech and non-speech, in children with ASD. In particular, Stroganova and colleagues have recently found a reduced pre-attentive processing of simple tones in the right-hemisphere in children with ASD, which was compromised by the left hemisphere processing (Stroganova et al., 2013). Additionally, two neuroimaging studies reported an increased activation of the left hemisphere in temporal regions in children with ASD during semantic task (Harris et al., 2006) and song processing (Lai et al., 2012). On the other hand, these findings contradict previous neuroimaging research that showed a lack of the leftward lateralization during speech and language processing in children with ASD and infants at risk for ASD, compared to neurotypical controls (Boddaert et al., 2004a, Redcay & Courchesne, 2008, Eyler et al., 2012, Seery et al., 2010). In particular, Redcay and colleagues showed the increased right hemisphere activation during speech processing in toddlers with ASD (Redcay et al., 2008). One can hypothesize that the finding of the left temporal lateralization of the mismatch effects in the ASD group could be partially due to the nature of the paradigm employed in the current study. For example, the presentation of the first speech sound might have activated to a certain extent the left hemisphere in the both groups. Following this, at later stages (N330, P600), both hemispheres might be engaged in processing both sounds which is required for the differentiation of stimuli in the TD group, while the ASD group fails to engage the right hemisphere. It is worth noting that, in contrast to speech stimuli utilized in the abovementioned studies (Redcay & Courchesne, 2008, Eyler et al., 2012), the stimuli utilized

in the current study are meaningless and are very closely matched on their physical characteristics. Therefore, it might be possible that the right temporal activity exhibited by the speech mismatch effects in the TD group reflect processing non-semantic speech characteristics, such as prosody, intonation and other socio-emotional aspects of speech and speech-like stimuli. On the contrary, children with ASD might engage compensatory mechanisms such as processing phonetic contrasts of stimuli in the left hemisphere, when distinguishing speech and non-speech sounds. In line with this hypothesis, Boddaert and colleagues showed that listening to complex synthetic speech-like stimuli can also elicit an abnormal cortical processing in children with autism in a similar fashion to speech (Boddaert et al., 2004a).

This finding of between group lateralization differences is consistent with a recent model suggesting two distint functions of left and right hemisphere for speech processing (Minagawa-Kawai et al., 2011). Additionally, to-date evidence suggests atypical processing of prosody and emotional prosodic cues in speech in children with ASD (Kujala et al., 2005, for the review, see O'Connor, 2012). Therefore, the lack of the right temporal activity in the ASD group in the current study might be explained by a diminished processing of socio-emotional aspects of speech, such as prosody and intonation, occurring in the right hemisphere. Additionally, it was shown that toddlers with ASD have a weaker interhemispheric functional connectivity in the language areas, including the inferior frontal gyrus (IFG) and the superior temporal gyrus (STG) (Dinstein et al., 2010). Thus the failure to engage the right hemisphere in the detection and classification of computerized speech as being different from speech might be also driven by the disrupted interhemispheric connectivity in this population.

Taken together, these findings provide further evidence for a selective impairment of the cognitive mechanisms of detection and evaluation of speech sounds in children with ASD. Additionally, together with the previous research, our findings indicate that speech processing abnormalities in children with ASD might be characterized by a diminished ability to distinguish auditory speech from computerized speech, as well as an impaired processing of social-emotional aspects of speech when identifying the difference between two categories of sounds. More specifically, we hypothesize that speech processing dysfunctions in ASD might be characterized by the failure to engage the right hemisphere when detecting the change from speech to a computerized stimulus, based on its social-emotional component, which is compromised by the left hemispheric processing of the physical and phonetic properties of speech and speech-like stimuli.

In summary, the current findings provide further evidence that children with ASD fail to detect speech when preceded by a computerized speech stimulus. These findings also indicate the neurophysiological imbalance between processing speech and non-speech sounds in children with ASD. In particular, children with ASD demonstrate an intact ability to distinguish non-speech sounds when preceded by speech which is presumably based on the physical (phonetic) characteristics of stimuli. Given that previous research suggested the impairment in social processing, including face and human action processing (Kaiser et al., 2010a, Webb et al., 2006, Webb et al., 2011, Oberman et al., 2005, Dapretto et al., 2006, Honaga et al., 2010), social attention (Klin et al., 2002, Pierce et al., 2011), as well as atypical non-social processing in children ASD (Webb et al., 2006, Dawson et al., 2002) and infants at risk for ASD (McCleery et al., 2009, Lloyd- Fox et al., 2013), we hypothesize that the speech processing abnormalities found in this study might potentially be associated with the imbalance between social and non-social processing in children with ASD. This notion is

consistent with previous suggestions that language and social functioning mechanisms are mediated by shared brain mechanisms and networks, including the superior temporal sulcus (STS) which has been found to be neuroanatomically and neurofunctionally impaired in autism (Redcay, 2008, Boddaert et al., 2004b). In line with this, the current results allow us to suggest that the speech processing abnormalities might be the part of broader social versus non-social processing dysfunctions in ASD.

CHAPTER 6:

GENERAL DISCUSSION

6.1 Thesis aims

This thesis had four main aims. Firstly, to explore the nature and the time-course of the mechanisms underlying hand and object touch observation. Secondly, to investigate the developmental aspect of these mechanisms in children from 4- to 5- years of age. Thirdly, I sought to further examine the specific mechanisms underlying the direct experience of touch, i.e. touch processing mechanisms in adults and children. Finally, I further examined the neural mechanisms underlying speech and computerized speech processing in typically developing children and children with ASD. This final Chapter will begin by summarizing the findings in each of the experimental Chapters (Chapter 2-5). Following this summary, I will further discuss the integration of the findings of this thesis with the existing literature. I will then move on to the discussion of the main methodological and theoretical limitations of the presented studies. Finally, in the general discussion I will provide directions for future research and the clinical implications in this specific research field, followed by a short conclusion.

6.2 Summary of the findings

6.2.1. Summary of the findings of Chapter 2: Streltsova &McCleery, 2014

In Chapter 2, I used ERPs to investigate the neural mechanisms underlying tactile mirroring, specifically those associated with the observation of touch of objects and humans in adult participants. The results revealed both 'early' and 'late' touch versus non-touch effects reflected in the ERP amplitude differences of N100, N250 and the Late Slow Wave Component (LSW:500-600 ms) recorded from the electrodes over the somatosensory cortex.

Additionally, human versus non-human effects were found and reflected in the latency differences of the following ERP components: somatosensory N100, P170, N250 components as well as visual-perceptual N170 and P250 recorded over the extrastriate visual areas. These findings further extend neuroimaging research of tactile mirroring mechanisms showing the somatosensory activations induced by the observation of both human and object touch (Ebisch et al., 2008, Ebisch et al., 2011; Schaefer et al., 2006, Schaefer et al., 2009, Keysers et al., 2004) by providing the evidence for the time-course of these mechanisms. More specifically, the observation of touch can modulate the somatosensory processing at early sensory-perceptual (N100), perceptual (N250) and late cognitive (500-600 ms) stages of information processing. These findings are also consistent with the results of previous electromagnetic and electrophysiological studies showing the modulation of the somatosensory cortex during the observation of touch at early (Bufalari et al., 2007) as well as late (Pihko et al., 2010) stages of information processing.

In addition to the amplitude touch versus non touch differences, latency differences of ERP components in the somatosensory area (N100, P170, N250) were identified for hand versus object touch observation. This suggests that the encoding of social information co-occurred with (N250) or preceded (N100, P170) the encoding of touch in the somatosensory area. These findings contribute to previous findings showing the involvement of the somatosensory cortex in processing social stimuli (Pitcher et al, 2008, Bolognini et al., 2011, see also Keysers et al., 2010). Additionally, in the temporo-parietal areas, larger amplitudes to hand versus object stimuli were identified for P170 and N250 components recorded over extrastriate visual areas, which is consistent with ERP studies suggesting differential processing of socially relevant stimuli, including human faces, at these components (Bindemann et al., 2008, Rossion & Caharel, 2011). These results are also in line with the

previous suggestion of the integration in the somatosensory and visual areas for processing social touch (Serino & Haggard, 2006, Haggard, 2007). Taken together, the present ERP findings suggest the encoding of social information in the somatosensory areas, either preceded by (at about 100 ms) or occurring simultaneously with (at approximately 170 and 250 ms) visual-perceptual processing of stimuli in the extrastriate visual areas.

6.2.2. Summary of the findings of Chapter 3

In Chapter 3, I applied a similar ERP paradigm to Chapter 2 to further examine the developmental aspect of tactile mirroring mechanisms underlying the observation of hand and object touch in 4- to 5- year old children**.** To address the gap in the developmental literature, I provided the first examination of the nature and the time-course of child touch versus non-touch observation mechanisms and discussed these findings in comparison to previous fMRI and MEG findings (Keysers et al., 2004, Ebisch et al., 2008, Ebisch et al., 2011, Pihko et al., 2010) and to the findings of Chapter 2 (Streltsova & McCleery, 2014). As a result, I found that hand and object touch observation mechanisms are recruited in children, and the time-course and the nature and these mechanisms appeared to be very similar to that in adults. More specifically, touch versus non-touch effects were exhibited in the amplitude differences of Late Slow Wave component (LSW: 600-700 ms) recorded from the electrodes over the somatosensory cortex. Additionally, hand versus object stimulus effects were identified in the amplitude of the somatosensory N100 as well as the latencies of the N170 component in the extrastriate visual areas. Therefore, these findings are consistent with the examinations of human and object touch in adults (Chapter 2) and provide the first evidence for somatosensory activations during the observation of touch in children. Importantly, the current findings demonstrate that tactile mirroring mechanisms, involved in the observation

of human and object touch are present in young children and are relatively similar to those in adults by five years of age.

Overall, these findings are in line with the previous fMRI (Keysers et al., 2004, Ebisch et al., 2008, Ebisch et al., 2011) and EEG/MEG findings (Bufalari et al., 2007, Pihko et al., 2010, Martinez-Jauand et al., 2012, Streltsova & McCleery, 2014) in adults showing somatosensory activations during action observation. It is worth noting though, that while there are similarities, there are also differences in adult versus child touch observation mechanisms. For example, no early touch versus non-touch effects which were identified in adults (N100, N250) were present in children. This can potentially be attributed to a generally slower encoding of touch in the somatosensory region in children. In both adults and children, it was found that the somatosensory cortex responds more to the observation of hand than to object stimuli. However, while in adults latency differences were identified indicating faster responses to human versus object stimuli in the somatosensory area, children showed larger responses to human versus object stimuli in the same area. Additionally, while stimulus type effects were largely bilateral in adults, an interaction between Stimulus and Hemisphere was revealed in children, indicating enlarged object processing in the left hemisphere in children.

Importantly, despite these relatively minor differences, the time-course and relative relations of ERP responses are largely similar in children and adults. Taken together with the previous studies, which have suggested the overall establishment of touch processing mechanisms in preschool and school-age children (Remijn et al., 2014, Björnsdotter et al., 2014) and early development of action mirroring mechanisms in infants and young children (van Elk et al., 2008; Nystrom et al., 2008, Nystrom et al, 2011; Marshall et al., 2011, Paulus et al., 2012, for a review, see Marshall and Meltzoff, 2014; Lepage & Theoret, 2006), the

current findings suggest the overall development of tactile mirroring mechanisms in 4- to 5-year old children.

6.2.3. Summary of the findings of Chapter 4

In Chapter 4, I further investigated whether the somatosensory activations revealed during touch observation in Chapter 2 and Chapter 3, are also present during direct tactile stimulation in adults and children. Time-frequency EEG analysis was employed to examine somatosensory cortical activity during rest and touch conditions. The somatosensory activity was revealed in the increased power (event-related synchronization) of somatosensory beta rhythms during the touch conditions in adult participants, when the participants were being touched either while they were looking at their own hand (visual-tactile condition) or looking at the screen in front of them (tactile condition), relative to rest. In contrast, somatosensory beta (15-24 Hz) modulation was absent in the child participants in both of these touch conditions compared to rest. The findings of Chapter 4 confirm the results of previous neurophysiological studies suggesting the synchronization of beta rhythms during tactile stimulation (Cheyne et al., 2003, Neuper and Pfurtsheller et al., 2001, Pfurtscheller et al., 2001). Taken together with the previous research suggesting the continuous maturation of neural tissues underlying different frequencies in children, as well as different patterns of spontaneous and movement related cortical rhythms in adults and young children (Cheyne et al., 2014, Rodríguez-Martínez et al, 2014), the current results suggest a further maturation of somatosensory beta in young children, which is reflected in somatosensory activity during the experience of touch. However, there could be also another methodology related explanation of the absence of beta modulation in children (see study limitation below and in Chapter 4).

In contrast to the previous research showing sensory-motor alpha (mu) suppression during action observation in both adults and children (Muthukumaraswamy et al., 2004, Perry et al., 2009, Streltsova et al., 2010, Lepage and Theoret, 2006), desynchronization of the somatosensory alpha rhythm was absent in both child and adult groups. It might be possible that, in contrast to action mirroring effects, tactile stimulation cortical effects are not reflected in somatosensory alpha (8-12 Hz) ERD/ERS effects. Notably, previous SEP studies examining somatosensory activity during touch utilized different procedure which involved induced tactile stimulation (Bufalari et al., 2007, Martinez-Jauand et al., 2012, Remijn et al., 2014). Therefore, it is impossible to directly compare the results of Chapter 4 with the previous findings on touch processing and tactile mirroring mechanisms in adults and children (Bufalari et al., 2007, Pihko et al., 2010, Martinez-Jauand et al., 2012, Streltsova & McCleery, 2014, Remijn et al., 2014). However, in light of the limitations of this study, one methodological explanation of the lack of alpha suppression seems also plausible. In particular, it might be an influence of occipital alpha, such as an increase of occipital alpha in the both touch conditions that masked somatosensory alpha activity. In future studies, it may be important to utilize source analysis techniques or independent component analysis (ICA) in an effort to separate posterior and central (somatosensory) alpha activity. The methodological limitations of Chapter 4 and other experimental Chapters are also discussed further below (Chapter 6, section 6.3).

In summary, the results of Chapter 4 provide evidence for somatosensory beta suppression during tactile stimulation in adults, but not in child participants. In the first instance, this seems to contradict the results of Chapter 3, which provide evidence for maturation of tactile mirroring mechanisms by 4- to 5- years of age. However, the somatosensory mechanisms uncovered in Chapter 4 might not reflect, or certainly are not

limited to, tactile mirroring mechanisms. In fact, these mechanisms are likely to reflect overall somatosensory processing during tactile stimulation. It is worth noting that, to date, only a few neuroimaging and electromagnetic studies have examined touch processing in children of a similar age (Björnsdotter et al., 2014, Gaetz et al., 2008, Xiang et al., 2004). For example, the results of a previous longitudinal neuroimaging study revealed similar activations in SI, SII, and insular cortex during tactile stimulation of a forearm and arm in all age groups, suggesting an overall establishment of processing of affective touch in preschool children (Björnsdotter et al., 2014). However, the methods utilized by Björnsdotter and colleagues and in Chapter 4 are different and, therefore, the results of the two studies cannot be directly compared. Firstly, Björnsdotter and colleagues used fMRI, providing much higher spatial resolution. Secondly, in Chapter 4, the neutral touch stimulation rather than affective touch was used, which might contribute to a possibly stronger activation of somatosensory cortices in Björnsdotter and colleagues' study. Additionally, in a MEG study, Xiang and colleagues investigated neuromagnetic activities induced by finger stimulation. The results of this study provided somatosensory activation map data indicating the differences between the somatosensory maps in children from 3- to 6- years of age and adults. In particular, the thumb functional area was found to be larger than that of the middle finger (Xiang et al., 2004). From these findings, one can suggest an ongoing maturation of some aspects of somatosensory processing in preschool and school-age children.

In sum, the findings of Chapter 4 allow to suggest that beta band activity associated with the direct experience of touch matures sometime between five years of age and adulthood. These findings do not contradict the results of Chapter 3 and the previous fMRI and MEG findings on the development of touch processing and tactile mirroring mechanisms in young children (Björnsdotter et al., 2014, Xiang et al., 2004, Pihko et al., 2007, Remijn et

al., 2014). Additionally, the current results contribute to this research demonstrating further maturation of a particular aspect of somatosensory processing, such as somatosensory beta activity, in preschool and school-age children. Interestingly though, in contrast to alpha suppression, cortical beta modulation has previously been found to be localized to the premotor cortex, not the somatosensory cortices (Hari and Samelin, 1997, Samelin and Hari, 1994). Therefore, the lack of beta modulation in children might also be attributed to general maturation of premotor and motor cortical activity rather than particular maturation of somatosensory activity in children. Additionally, the absence of beta activity can be attributed to a methodological choice of the baseline which was shown to have an effect on the findings of modulation of central alpha (mu) rhythms during action observation in infants and children (for a review, see Cuevas et al., 2014). Finally, as mentioned earlier, absence of somatosensory alpha suppression was observed in both adult and child groups, and therefore, is unlikely to be attributed to the immaturity of child touch processing.

6.2.4. Summary of the findings of Chapter 5

Chapter 5 examined the neural correlates underlying speech (social) and computerized speech (non-social) processing in typically developing children and children with ASD. In this Chapter, we used a paired repetition ERP paradigm to examine the processing of repeated (match) and non-repeated (mismatch) speech and computerized speech sounds, presented in pairs. Specifically, the presented stimuli were pairs from either the same category (speech, computerized speech) or different categories. The results showed that both participant groups exhibited match/mismatch ERP effects at approximately 330 ms and 350 ms, reflected in the amplitude differences of N330 and P350 components recorded over the temporal and central

regions, respectively. These findings suggest that the categorisation/detection of speech followed by a computerized sound in the central and temporal areas is present in both groups. However, differences between the groups were found in the lateralization of brain responses for the N330 component. In particular, while the typical children showed bilateral responses, the N330 effect was present only in the left hemisphere in children with ASD. Taken together, these particular findings of Chapter 5 suggest the failure to engage the right hemisphere for speech versus computerized speech processing in children with ASD. Based upon previous research suggesting a degree of distinction between left and right hemisphere processing for speech (Arimitsu et al., 2011, Minagawa-Kawai et al., 2009, Minagawa-Kawai et al., 2011), I further suggest that the failure to engage the right hemisphere most likely reflects an impaired right-hemispheric processing of social and emotional aspects of speech in the classification of speech sounds when followed by computerized speech in children with ASD.

Finally, it was revealed that typically developing children exhibited match/mismatch effects for computerized speech followed by speech at approximately 600 ms over central and temporal areas, reflected in amplitudes of the N600 and the P600 components, while this effect was absent in the ASD group. On the contrary, the ASD group exhibited the N600 mismatch effect in the condition where speech was followed by a computerized stimulus. Taken together with previous ERP findings (Ceponiene et al., 2003; Kuhl et al., 2005; Lepisto et al., 2005, Lepisto et al., 2006; Whitehouse & Bishop, 2008), these results further suggest the intact processing and evaluation of non-speech sounds preceded by speech, and diminishment of late cognitive evaluation of speech sounds, when preceded by non-speech sounds, in children with ASD.

Overall, the findings of Chapter 5 shed more light on the nature of abnormalities in processing speech and non-speech sounds in children with ASD. ERP component differences indicated both lateralization differences in the classification of computerized speech and speech sounds (N330), and impaired late cognitive evaluation (P600, N600) of speech when preceded by computerized speech in children with ASD. It is worth noting that the timings and temporal distribution of these between-group ERP effects are consistent with previous ERP research on speech and non-speech processing in ASD (Ceponiene et al., 2003; Kuhl et al., 2005; Lepisto et al., 2005, Lepisto et al., 2006; Whitehouse & Bishop, 2008). In general, these results are consistent with previous findings suggesting deficient classification and processing of speech reflected in late cognitive ERP components (Ceponiene et al., 2003, Kuhl et al., 2005, Lepisto et al., 2005, Lepisto et al., 2006). In addition, as mentioned above, the results of Chapter 5 demonstrate that the order of the sound presentation matters for the discrimination of speech and non-speech sounds. More specifically, children with ASD can identify and process a computerized speech sound coming after a speech sound, but fail to distinguish a speech sound from a preceding computerized speech sound.

The results of Chapter 5 contribute to the findings of the abovementioned ERP studies suggesting an atypical leftward lateralization for processing of computerized speech sounds preceded by speech. It is worth noting that, due to the nature of the current paradigm (i.e., speech stimuli were presented shortly after non-speech sound and vice versa), it is likely that the lateralization found for the N330 non-speech mismatch effect reflects discrimination between speech and non-speech, rather than just an atypical processing of a computerized speech sound alone (see more Chapter 5, discussion section and Chapter 6, section 6.2.5). Thus the atypical lateralization of the N330 mismatch effect might represent the failure to engage the right hemisphere in differentiation of speech and computerized sounds in ASD.

This notion is consistent with previous neuroimaging findings showing an increased activation of the left hemisphere for speech and song processing in children with ASD (Harris et al., 2006, Lai et al., 2012). Therefore, the lack of right temporal activity in the ASD group found in Chapter 5 might be explained by the lack of processing prosody and social-emotional cues of stimuli, which is compensated by the reliance on the processing of physical characteristics of speech and non-speech in the left hemisphere.

It is important to note here that despite the differences in objectives and aims of Chapters 2-4 and Chapter 5, taken together, the findings of Chapter 5 indicate specific social processing difficulties in children with ASD, by demonstrating speech processing abnormalities. At the same time, mirroring and touch processing mechanisms that have been the subjects of the research in Chapters 2-4 certainly represent an important aspect of social-cognitive development that have been previously found to be impaired in ASD (Oberman et al., 2005, Bernier et al., 2007, Oberman et al., 2013, Bastiaansen et al., 2011, Dapretto et al., 2006; Honaga et al., 2010, Cascio et al., 2012, Cascio et al., 2013, Puts et al., 2014; see also Chapter 1, section 1.5.3). In summary, the findings of Chapter 5 suggest lack of reliance on social-emotional cues in the classification of social (speech) and non-social stimuli (computerized speech), as well as the diminishment of cognitive evaluation of social stimuli (speech) when preceded by non-social stimuli (computerized speech) in children with ASD. Therefore, there is a significant overlap in the research in Chapter 5 and the previous chapters. Specifically, while the results of Chapter 2-4 generate increased understanding of the nature of neural mechanisms for typical development of mirroring mechanisms and touch processing, the results of Chapter 5 shed more light on the atypical development of another important aspect of social processing, speech processing, in the disorder of social cognition, autism spectrum disorder.

6.2.5. Conclusions

In summary, the present findings addressed the aims and hypothesis of the current thesis, which is outlined in the Introduction to the thesis. The present results demonstrate the nature and the time-course of specific neural mechanisms recruited during the observation of human versus object touch in adults and children. They show that these mechanisms, which are most likely to reflect tactile mirroring mechanisms, appear to be present and very similar to adults in typically developing children by 4- to 5- years of age. Additionally, the results of the current thesis suggest that somatosensory beta activity (15-24 Hz) recruited during tactile stimulation is likely to undergo some maturation in the somatosensory and/or motor cortical areas in 4- to 5- year old children, relative to adults. Finally, the current findings demonstrate the event-related potential correlates for specific speech processing abnormalities in 4- to 6-year old children with autism, which might be the part of a broader dysfunction of social-cognitive processing in ASD.

6.3 Theoretical and methodological limitations

Despite the importance and originality of the research presented in this thesis, it is important to address some theoretical and methodological limitations of the presented studies. These limitations include limitations of the experimental paradigms used in Chapters 2-5, general EEG technique limitations, characteristics of the participant samples in Chapters 3-5, as well as limitations for experimental data interpretation, particularly for Chapter 4 and Chapter 5.

One possible general limitation in all experimental Chapters is related to the low spatial resolution of the EEG technique employed in the current thesis. The area of the electrodes selected for the analysis in Chapters 2-4 was over the somatosensory cortex, which is likely to represent the activity in the primary somatosensory cortices and adjacent areas. Similarly, in order to investigate speech processing, the clusters of electrodes were selected in the temporal and frontal-central regions, presumably involved in auditory perceptual and more cognitive speech processing, respectively. Despite the growing body of MEG and EEG evidence showing the effects over the same areas for speech processing (Ceponiene et al., 2003; Kuhl et al., 2005; Lepisto et al., 2005, Lepisto et al., 2006; Whitehouse & Bishop, 2008), the lack of spatial localization of the somatosensory activity revealed in Chapters 2-4 as well as central-temporal activity related to speech processing in Chapter 5 remains one potential limitation of the current thesis. In future studies, it might be important to address this issue by applying EEG source analysis techniques in conjunction with individual participant magnetic resonance imaging (MRI) scans, in conjunction with the current ERP and EEG paradigms.

The second methodological limitation of the present thesis is related to the experimental procedures employed in each of the experimental Chapters. Specifically, in Chapter 2 and Chapter 3, the presented stimuli were not rated on the clarity of the depicting movement and more importantly, the presence of touch, by the same or different participants before the EEG experiment. It is important noting though that a questionnaire was used for adult participants after the EEG experiment in Chapter 2, where the participants were asked whether the presence or absence of touch in the videos was obvious in the videos. All included participants confirmed that they could differentiate between touch and non-touch in each video. However, the fact that children might interpret the same videos differently was not taken into account in Chapter 3 in which, due to time limitations, child participants were not questioned about the clarity of the videos showing touch and non-touch. Although the final stimuli were the same in Chapter 2 and Chapter 3, and were selected from a greater pool of videos based on the similarity of movement trajectory and clarity of touch, there is no further direct proof that child participants in Chapter 3 were able to differentiate between touch and non-touch in certain videos.

The experimental paradigm of Chapter 2 involved priming via tactile stimulation employed prior to and after the observation of the videos in adult participants. The reason for including this procedure before the first and second part of ERP recording in adults in Chapter 2 was to ensure that the activity measured over the somatosensory cortex represents, or includes, the mirroring activity which was previously measured as an overlap of activations in the same sensorimotor and somatosensory cortical areas occurred during the observation of action/touch and action execution/tactile stimulation (Iacoboni et al., 1999, Buccino et al., 2001, Dinstein, 2007, Keysers et al., 2004, Ebisch et al., 2008, Gazzola and Keysers, 2009). However, in this case participants were also familiarised with objects

presented later in the videos. Therefore, there is a possibility of this priming having an effect on the ERP results of Chapter 2. To avoid this, the tactile stimulation was carried out at the end of the experiment in children (Chapter 3).

The main methodological limitation of Chapter 4 is the performed tactile stimulation. This stimulation was performed with three different objects, each of them inducing different type of touch and amount of pressure on the palm of the hand and outer forearm. Additionally, the stimulation was not synchronized with the EEG recording, and no real marker indicating the starting point and the end of the tactile stimulation was used (see more Chapter 4, discussion section). In this case, it might have been possible that the segments included in the EEG data analysed did not include touch. This, taken together with relatively small amount of artefact free EEG data for each condition (approximately between 20 and 40 sec), could also have contributed to the lack of somatosensory alpha suppression in both adults and children in Chapter 4. On the other hand, the beta synchronization found in adult participants might represent an effect that usually occurs after the tactile stimulation, that is similar to a post-movement beta rebound (Avanzini et al., 2012, Hari, 2006, Neuper et al., 2006), rather than reflecting the somatosensory modulation induced by the tactile stimulation. These limitations can be however addressed in the future research by introducing some modifications in the experimental procedure (see Chapter 6, section 6.4).

Another methodological limitation of the present thesis is the presentation of auditory stimuli in Chapter 5. In particular, the interval between the first and second speech or non-speech stimuli (T=50 ms) was very short compared to between the inter-trial interval (IT=475-625 ms). Although the presence of long inter-trial intervals is important for the correct implementation of the ERP procedure (Luck, 2005), the ERPs in this case, when time-locked to the first stimuli, certainly represent evoked responses to both stimuli of the same or

different category. Considering the timing of the ERP effects found in Chapter 5 though, it is likely that match/mismatch ERP effects reflected in the late cognitive components (N330, N600, P600) represent classification and cognitive evaluation of the second speech or non-speech stimuli. However, for this evaluation to take place, prior processing of the first stimulus is required. Therefore, the nature of the procedure makes it difficult to disentangle clearly the neural responses for speech versus non-speech processing. This however has been taken into account into the interpretation of findings of Chapter 5, where we discuss the underlying mechanisms of the match/mismatch effects in the conditions where speech was followed by non-speech, and vice versa. Notably, the results showed that the order of the stimuli presentation matters for successful speech detection in children with ASD, i.e. children with ASD can discriminate a non-speech sound from preceding speech sound, but showed an impaired later cognitive processing of speech sound when preceded by a non-speech sound. Thus the findings of Chapter 5 suggest that, despite some difficulty in interpreting the underling processing in mismatch conditions, the experimental paradigm was successful in depicting specific speech processing abnormalities in children with ASD.

Another potential limitation of the experimental paradigm in Chapter 5 is the concurrent presentation of visual (silent video) and auditory stimuli. It has been suggested that the concurrent presentation of visual stimuli during the auditory ERP recording helps to reduce artifacts, created by body and eye movements (Lloyd-Fox et al., 2013). It is worth noting though that visual stimuli in cartoon videos used in Chapter 5 did not contain associations with presented auditory speech and non-speech sounds and were not synchronised with them. Despite this precaution, it was not possible to avoid the fact that cartoon characters in presented videos were interacting and talking with each other. Therefore, we cannot be certain that the visual stimuli, i.e silent videos, might have included

potential imagery of an ongoing conversation and might have affected cortical ERP responses to auditory speech and non-speech sounds.

The final limitation of the current thesis is related to the child participants' sample recruited in Chapter 3-5. In particular, while participants included in Chapter 2 and Chapter 4 were all right-handed, a few left-handed participants were included in the analysis in Chapter 3 and Chapter 5. It is worth noting that a between-subject design was employed in Chapter 3 and 5. This means that the number of left-handed participants was made equal in children, who watched objects and human hands being touched (Chapter 3), as well as in typically developing children in TD CA group and children with ASD (Chapter 5). However, no further assessment of handedness was carried out in children, and handedness was only reported by a parent. Additionally, there were two left handed participants in TD VA group compared to three left-handed participants in the ASD group (Chapter 5). Therefore, the TD VA and ASD groups were not exactly matched on handedness, and it is also possible that the participant groups in Chapters 3-4 were not fully matched on handedness. This however does not seem a likely explanation for the lateralization differences found in Chapter 5 as the included results were consistent between TD VA and TD CA comparison groups. It is also unlikely that inclusion of four left-handed participants (two in each comparison group) in Chapter 3 and potential inclusion of one or two left-handed participants in Chapter 4 had any impact on the ERP/EEG findings in these Chapters, as tactile mirroring and touch processing mechanisms did not demonstrate a particular lateralization in previous fMRI studies in both adults and children, when touch was applied to both hands (Keysers et al., 2004, Ebisch et al., 2008, Ebisch et al., 2011, Björnsdotter et al., 2014). However, to completely exclude this possibility, in the future studies it might be important to examine the neural mechanisms

studied in Chapters 3-5 in right-handed participants, as well as to conduct an assessment of handedness in all 4- to 6- year old children who participated in the current studies.

Finally, four children included in the ASD group in Chapter 5 did not have a clinical diagnosis of ASD. This was due to the prolonged procedure of the clinical referral to a specialist by the National Health Service (NHS) in the greater Birmingham area and other regions in the UK. It is not uncommon for some children not to be diagnosed before the age of six or more in this particular area of the UK. Due to the time constraints of this project, four children who had been referred to a specialist but had not yet received a formal diagnosis were included in the analysis. As a result, ASD diagnosis for these children was based on the results of the Autism Diagnostic Observation Schedule (ADOS-G) in combination with the results of Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003), while the remaining ten children also met a cut-off criteria on ADOS-G combined with SCQ, in addition to their formal diagnosis. It is worth noting that the use of ADOS-G combined with SCQ, or ADOS-G alone was found to demonstrate higher specificity and sensitivity and therefore, a higher predictive value, in a large sample of 20- and 40- month old children at high risk for ASD (Oosterling et al., 2010) and older children with ASD (Corsello et al., 2007), than compared to other methods such as Autism Diagnostic Interview-Revised (ADI-R) or a combination of ADOS-G with ADR-I. On this basis, it is rather unlikely that the inclusion of a small number of participants without external confirmation of their clinical diagnosis may affect the current results.

6.4 Future directions and clinical implications

The current ERP and EEG data contribute to the growing body of evidence investigating mirror functioning and tactile processing in young children (Xiang et al., 2004, Björnsdotter et al., 2014, Pihko et al., 2009; Lepage and Theoret, 2006, Remijn et al., 2014), and speech processing in typically developing children and children with ASD (Ceponiene et al., 2003; Kuhl et al., 2005; Lepisto et al., 2005, Lepisto et al., 2006; Whitehouse & Bishop, 2008). However, some of the abovementioned limitations of the experimental procedures and current findings can be further addressed in future research. In particular, it would be interesting to explore whether the nature of tactile stimulation employed in Chapter 4 had any impact on the findings of the somatosensory alpha and beta modulation. For this purpose, a thorough examination of EEG responses to tactile stimulation of the glabrous part of the hand, which has more tactile afferent receptors (Rolls, 2010), synchronized with the EEG recording might be a subject for future research of the development of the tactile processing in young children. It is worth noting though that a particular strength of the methods employed in Chapter 4 is the use of real touch performed by a human as opposed to robot or SEP electrical stimulation utilized in previous studies in adults and children (Bufalari et al., 2007, Martínez-Jauand et al., 2012, Remijn et al., 2014). On the other hand, in order to completely synchronize EEG recording with tactile stimulation, a robot might be required to perform the stimulation. Given that machine (robot) and real touch might induce different somatosensory activity, a thorough examination of the somatosensory responses to robot versus real touch might be another interesting subject for future research of the development of touch processing.

Although a particular strength of EEG is its high temporal resolution, which allowed the exploring of the time-course of the observation of touch (Chapter 2 and Chapter 3), it provides a poor spatial localization of somatosensory activity. Therefore, it might be of value to employ neuroimaging techniques such as fMRI or functional near-infrared spectroscopy (fNIRS) to localize the somatosensory ERP activity found during touch observation and tactile stimulation in young children. Previous EEG research demonstrated that, similarly to adults and children, young infants also exhibit sensorimotor activity during action observation (Nystrom et al., 2008, Nystrom et al., 2011; van Elk, 2008; Stapel et al., 2010) and touch processing (Gondo et al., 2001, Rigato et al., 2014, Pihko et al., 2009). In light of these previous findings suggesting an early development of mirroring and tactile processing, the present findings have the potential to be further explored in neuroimaging and electrophysiological studies in younger children and infants. In particular, fNIRS which combines a good temporal resolution with a better spatial resolution than EEG is also one of the most child-friendly and increasingly adopted methods to study functional brain activation in infants and children (for a review, see Lloyd-Fox et al., 2010). For these reasons, the implementation of fNIRS could be particularly useful in future research further investigating somatosensory activity during the observation of touch and tactile processing in young infants.

The experimental procedures as well as the findings of this thesis have several implications for future clinical research. Specifically, the ERP paradigm used in Chapter 3 opens up the opportunity to examine the mechanisms and time-course of tactile mirroring in children with autism who, as previous evidence has suggested, exhibit impairments and atypicalities in action mirroring mechanisms (Becchio & Castiello, 2012, Oberman et al., 2013, Enticott et al., 2012). Notably, touch represents an important aspect of social

interactions, especially early in life. There is some recent evidence of impaired touch processing and diminished response to neutral and affective touch and impaired tactile processing in autism (Cascio et al., 2012, Cascio et al., 2013, Puts et al., 2014, for review, see Cascio et al., 2010). Therefore, the experimental procedures used in Chapters 2-4 can also be adapted for exploration in children with ASD and infants with high-risk for ASD. This would broaden our knowledge and understanding of the nature of impairments of social processing in ASD and allow further development of early screening methods and diagnostic tools enabling diagnosis of these children before 3 years of age (Chawarska et al., 2007, Chawarska et al., 2009, see also McCleery, Stefanidou, & Graham, 2011). Finally, the findings of Chapter 5 suggest a specific neural impairment of detection of speech from non-speech, as well as atypical lateralization for processing speech and non-speech, in children with ASD. Future research is however needed to provide a clearer picture of the distinct role of atypical speech and non-speech processing mechanisms which might underlie the impairments of speech and non-speech classification in children ASD. Taking into account the previous research suggesting an impairment of social processing (Kaiser et al., 2010, Oberman et al., 2005) and atypical (enhanced) non-social processing in children with ASD and infants at risk for ASD (Webb et al., 2006, McCleery et al., 2009, Lloyd- Fox et al., 2013), in future research it might be important to investigate further the imbalance of speech and non-speech processing in ASD without confounding of attentional orienting as in previously employed MMN paradigms (Ceponiene et al., 2003, Kuhl et al., 2005, Lepisto et al., 2005, Lepisto et al., 2006). This particular research may provide more information about the nature of social versus non-social impairments in ASD and deepen our understanding of the relationship between the impairment of social-cognitive functioning, including mirror functioning (Oberman et al., 2005, Oberman et al., 2013, Enticott et al., 2012, Dapretto et al., 2006,

Bastiaansen et al., 2011, Honaga et al., 2010) and speech and language impairment in ASD (Minagawa-Kawai et al., 2009, Minagawa-Kawai et al., 2011, Redcay, 2008).

6.5 Thesis conclusion

In summary, this thesis set out to explore four main aims. Firstly, I investigated the nature and time-course of neural mechanisms underlying the observation of both hand and object touch. Following this, the development of the neural mechanisms for the observation of human and object touch was explored in young children. The findings demonstrated that tactile mirroring mechanisms are relatively developed in 4- to 5- year old children. Thirdly, the somatosensory activations underlying tactile processing in adults and children were explored. The findings revealed the modulation of somatosensory beta (15- 24 Hz) activity during touch in adults, but not in children. Finally, the neural mechanisms underlying processing of speech and computerized speech sounds in typically developing children and children with ASD were explored. These electrophysiological results suggest an impaired classification of speech from preceding computerized speech sounds and atypical lateralization of speech processing in children with ASD.

To conclude, this work has expanded our knowledge in the areas of the development of social and non-social processing, more specifically, tactile mirroring and touch processing mechanisms in typical development, and speech processing in young children with autism. In future research, it will be important to further explore the development of tactile mirroring and touch processing in typical development in infants, as well as atypical development in infants at high-risk for autism and children with autism. Finally, further work is needed to explore the nature of speech versus non-speech processing dysfunctions in autism, to discover

more about the links between social-cognitive impairments and language and speech impairment in ASD.

APPENDICES

APPENDIX A1

Consent form for adult participants who took part in Study 1 presented in Chapter 2.

University of Birmingham Infant and Child Laboratory Research Study

"Children's and Adult's Brain Processing of Touch" - Consent for Adult

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

The purpose of this study is to help us understand how normal adults and children process sensory touch information such as human and non-human touch. Your participation will prepare us to study touch processing in children and infants at risk of psychiatric disorders in the future.

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

Joseph McCleery, PhD, Alena Streltsova, 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 in this study because you are a normal adult. 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 come to our laboratory for approximately 1 hour and the following will happen.

We will measure your brain activity using a sensor net that has electrodes sewn into it. The electrodes measure the electricity that your brain generates. The electrodes will not hurt. We will place the net on your head, and squirt a salt-water solution onto sponges that touch your head. The salt-water solution is not toxic or dangerous. You will then sit in a quiet, dimly lit room in front of a computer screen where short videos of people and things being touched will be shown to you. Your task will be to just watch the stimuli attentively, and you may be asked to press a button when you see a particular video presented. You may also be videotaped during these sessions so we can determine when you were attending to the visual stimuli after you have participated. Before or after the sessions, the experimental will use different objects, such as **feathers** and **plastic arm massagers**, to touch the palm of your hand and your arm so that we can measure your brain's response to your body being touched.

Are there any risks associated with participating in this study?

There are no known risks associated with the brainwave recordings. You may become bored during the experiment.

What are the benefits of this research study?

There will not be any benefit to you from participating in this study. You should know that the EEG procedure is not the same as you 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 health. The investigators, however, will learn more about how children and adults process visual tactile stimuli.

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

The records of this study will be kept private. Your name and the other personal details you provide will be stored. However, research data will only be identified by your 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 receive 60 minutes of course credit or be paid **£ 6** for your participation in this study. The researcher may also 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, and I can stop participation at any time by letting the researchers know that I would like to do so. If I refuse to participate or choose to drop out of the study at any time, I understand that this decision will not affect my relationship with the University of Birmingham. I have received a copy of this consent form. I am signing this consent form before participating in any research activities. I give permission for my participation in this study.

If you have any questions about this study, you may contact the researchers by email or by telephone:

_____

Date

_____ _____

Name of Participant Signature of Participant

_____ _____

Name of Researcher / Witness Signature of Researcher / Witness

APPENDIX A2

Consent form for parents of typically developing children who took part in Study 2 presented in Chapter 3.

University of Birmingham Infant and Child Laboratory Research Study

"Children's and Adult's Brain Processing of Touch" – Parent Consent for Infant/Child

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

The purpose of this study is to help us understand how normally developing children and adults process sensory touch information, such as human and non-human touch. Your child's participation in this study will prepare us to study touch processing in children and infants at risk of psychiatric disorders in the future.

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

Joseph McCleery, PhD, Alena Streltsova, 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 1 visit 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 videos of objects touching a person's hand or arm, and objects touching other objects. Before or after the video presentations, the experimental will touch the palm of your child's hand and the lower part of your child's arm gently with different objects, such as **feathers** and **plastic arm massagers**, so that we can record his/her brain's response to being touched. The touching will not hurt your child and you will be in the room with her/him while she/he is being touched.

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 videos or they may get tired or bored during the testing. 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 sensory information, such as human and non-human touch.

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 cost 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, and I can stop participation at any time by letting the researchers know that I would like to do so. 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 have received a copy of this consent form.I am signing this consent form before participating in any research activities. I give permission for my/my child's participation in this study.

If you have any questions about this study, you may contact the researchers by email or by telephone:

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

APPENDIX A3

Consent form for parents of typically developing children who took part in Study 4 presented in Chapter 5

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, Alena Streltsova, 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

Consent form for parents of children with autism who took part in Study 4 presented in Chapter 5.

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, speech) and sounds made by things (e.g., helicopter, non-speech).

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

Joseph McCleery, PhD, Alena Streltsova, 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 2-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 £10.00for 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 B1

Questionnaire for parents of children with autism used in Study 4 in Chapter 5.

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

Thank you very much for agreeing to take part in our study at 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 B2

Questionnaire for parents of typically developing children used in Study 4 in Chapter 5.

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: _____

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

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