Neural Activation During Emotional Face Processing in Adolescents with Autism Spectrum Disorders

by

Rachel Leung

A thesis submitted in conformity with the requirements for the degree of Masters of Arts
Graduate Department of Psychology
University of Toronto

© Copyright by Rachel Leung 2012
Neural Activation during Emotional Face Processing in Adolescents with Autism Spectrum Disorders

Rachel Leung

Masters of Arts

Graduate Department of Psychology
University of Toronto

2012

Abstract

Impaired social interaction is one of the hallmarks of autism spectrum disorders (ASDs). Emotional faces are arguably the most critical visual emotional stimuli and the ability to perceive, recognize, and interpret emotions is central to social interaction and communication as well as healthy development. There is however, a paucity of studies devoted to neural and cognitive mechanisms underlying emotional face processing in adolescents with ASD. Through an implicit emotional face processing task completed in the MEG, we examined spatiotemporal differences in neural activation during angry and happy emotional face processing. Results suggest atypical frontal involvement in ASD adolescents during angry and happy face processing. In particular, orbitofrontal activation in participants with ASD was found to be delayed but greater in amplitude, relative to controls.
Acknowledgments

First and foremost, I would like to express my immense gratitude and sincere thanks to my supervisor, Dr. Margot Taylor, and my committee members, Dr. Mary Lou Smith and Dr. Elizabeth Pang, for all of your support and guidance. Your mentorship has been vital to my growth in research.

Sincere thanks to Dr. Evdokia Anagnostou and her research team at Holland-Bloorview Kids Rehabilitation Hospital for all their help with ADOS administrations and training as well as Dr. Eva Mamak for her neuropsychological training.

Special thanks to Dr. Elizabeth Kelley, who first gave me the opportunity to be involved in autism research.

I am endlessly grateful for the indispensable support of my wonderful colleagues and friends, Krissy Doyle-Thomas, Rina Goukon, Yuwen Hung, Sarah Yao Lin, Lydia Sproule, Samantha Trelle, and Sin Varatharajah. Rina and Sarah were pillars of moral support and mentors in domains beyond academics. Sin was essential to the completion of this thesis, due to her breadth of knowledge and ingenuous support schemes.

Many thanks to Marc Lalancette, Hamzah Qureshi, Ruth Weiss, and Tammy Rayner for all their support in data acquisition and analyses.

Thank you to my family and friends for their enduring support.

Lastly, immense thanks to and in memory of Dr. Jeanette Holden, whose passion for research in autism has and will continue to be a source of inspiration.

Rachel Leung was supported through a studentship, fully or in part, by the Matching Funds Program, Hospital for Sick Children Foundation Student Scholarship Program.
# Table of Contents

Acknowledgments ........................................................................................................ iii

Table of Contents ........................................................................................................ iv

List of Tables ................................................................................................................... vii

List of Figures ................................................................................................................ viii

Chapter 1 Introduction .................................................................................................. 1

1.1 Conceptualizing emotional face processing ............................................................... 1

1.2 Autism Spectrum Disorders ....................................................................................... 2

1.3 Typical development of emotional face processing ..................................................... 3

1.4 Emotional face processing in ASD ........................................................................... 4

1.5 Anger processing in ASD ......................................................................................... 6

1.6 Happy processing in ASD ...................................................................................... 8

1.7 Adolescence ............................................................................................................. 9

1.8 Neural substrates of typical emotional face processing .............................................. 11

1.8.1. Source localization of typical emotional face processing ................................. 11

1.8.2. Temporal profile of neural activation during typical emotional face processing ... 12

1.8 Neural substrates of emotional face processing in ASD ........................................ 13

1.8.1. Source localization of emotional face processing in ASD ................................. 13

1.8.2. Temporal profile of neural activation during emotional face processing in ASD .. 14

Chapter 2 Objectives and Hypothesis .......................................................................... 16

Chapter 3 Methods ...................................................................................................... 18

3.1 Participants ............................................................................................................ 18

3.2 Measures of Autistic Symptomatology ................................................................... 18

3.3 Behavioural Assessments ...................................................................................... 19
3.4 Tasks and Procedures

3.4.1 Cognitive assessments

3.5 MEG Emotional Face Task

3.5.1 Stimuli

3.5.2 Procedure

3.6 MEG Data Acquisition

3.7 MEG Data Processing

3.8 Anatomical MRI Acquisition

3.9 Anatomical MRI Processing and Co-registration

3.10 Behavioural Analyses

3.11 MEG Analyses

Chapter 4 Results

4.1 Behavioural assessment results

4.2 Emotional Face Task behavioural results

4.3 Neuroimaging results

4.3.1 Global field power plots

4.3.2 Within and between group analyses of frontal activity

4.3.2.1 Angry faces

4.3.2.2 Happy faces

Chapter 5 Discussion

5.1 Parental response forms

5.2 Behavioural findings

5.3 Source localization in typically developing adolescents

5.4 Early emotional differentiation during emotional processing in control adolescents

5.5 Atypical spatiotemporal profile of emotional face processing in ASD
5.5.1 Between group comparisons towards happy faces ........................................... 42
5.5.2 Between group comparisons towards angry faces ......................................... 43
5.5.3 Spatiotemporal profile of orbitofrontal activation in response to angry faces..... 44
5.6 Summary of findings ......................................................................................... 44
5.7 Limitations and Future Directions ..................................................................... 45
5.8 Conclusions ........................................................................................................ 46
References .............................................................................................................. 48
List of Tables

Table 1. BRIEF, CADS, RBS-R, and SRS Parent Response Forms scores.

Table 2. Response latencies on the Emotional Face Task.

Table 3. Locations of significant ($p < .05$, uncorrected) peak activations for adolescents with ASD and controls in response to (a) angry and (b) happy faces.

Table 4. Locations of significant ($p < .05$, uncorrected) peak activations for ASD versus controls in response to angry faces (a) and ASD versus controls in response to happy faces (b).
List of Figures

Figure 1. Global field power plots for (a) angry and (b) happy face conditions between groups.

Figure 2. Global field power plots show comparable neural activity across all emotion conditions in the ASD group.

Figure 3. Significant areas of activation in within-group analyses (rows 1 and 2) in comparison to significant between-group analyses (row 3) to a) angry and b) happy faces.
Chapter 1
Introduction

The development of emotional processing is integral to children’s ability to acquire social skills. In autism spectrum disorders (ASD), impaired social skills and interactions are one of the diagnostic indices of the disorder, and behavioural observations of deficits in emotional processing have been correlated with abnormalities in underlying neural regions. Asynchronous development of emotional recognition (i.e., earlier recognition of happy relative to negative affect) in typically developing individuals is well established (Markham & Adams, 1992; De Sonneville et al., 2002) and neuroimaging findings have demonstrated the shifting involvement of different neural networks over the course of development (Hung, Smith, & Taylor, 2012; Killgore & Yurgelun-Todd, 2007; Monk, et al., 2003). Hence, investigating the temporal and spatial properties of neural activation during emotional processing during the course of development in ASD is of particular interest as it carries the potential to elucidate the neuropathology of social deficits in ASD and offer insight into the functional specialization of rapid emotional processing in both clinical and typical populations. The value of the present study exists in its identification of neural regions involved in emotional face processing development in the adolescent ASD population as well as timing information of the involvement of these regions. Understanding the neurobiology underlying different patterns of emotional and face processing will have important clinical ramifications in terms of developing interventions for optimising emotional processing skills, and thereby social functioning, in children with ASD.

1.1 Conceptualizing emotional face processing

During the course of everyday life, the human senses are constantly surrounded by a myriad of stimuli in the environment. To prevent being inundated with information, cognitive mechanisms are in place to assess external stimuli, detect those that are relevant to the task or interests at hand, and selectively attend to those stimuli. The human face is perhaps the most important visual stimulus, offering a wealth of social information, for which intact processing is critical to healthy development and successful social interactions. For young children who have
not yet acquired fluent speech, perceiving and processing facial expressions of emotion is one of the first tools they have for social interaction and communication.

The ability to extract the social significance of expressive faces is critical for successful social interactions as it facilitates the understanding of other’s mental states and intentions as well as the appropriate behaviour to reciprocate. Emotional face processing appears to be innate and universal (Ekman & Friesen, 1971; Meltzoff & Moore, 1977). Preschoolers’ abilities to accurately perceive and interpret emotional faces have been found to be predictive of both social behaviour and academic achievement (Izard et al., 2001; Mostow et al., 2002). It is important to note that emotional face processing occurs as a two-fold process involving perceptual processing, which is based upon discriminating between emotional facial expressions by identifying the configuration of facial features, and knowledge-based processing whereby the perceiver recognizes the affective signal by assigning social significance to the perceived expression (Adolphs, 2002). Successful knowledge-based processing is in turn dependent upon the perceiver being able to conceptualize the emotion, assign a lexical label to the emotion, and perceive a behavioural response to the emotional stimuli (Adolphs, 2002). Discriminating between these distinct processes will aid in answering the question of whether emotional face processing is impaired in ASD, and if so, whether it is due to deficits in perception or interpretation.

1.2 Autism Spectrum Disorders

Autism spectrum disorders (ASD) is a collective term for a group of complex neurodevelopmental disorders in which the features of the disorder may be similar but the severity of impairment in various domains (i.e., emotional, motor, social) can range from mild to severely disabled. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR, APA 2000) currently recognizes five disorders under the ASD umbrella. While there are some inconsistencies as to the inclusion of Rett’s Syndrome and Childhood Disintegrative Disorder due to discrepancies in prevalence and developmental trajectory, the three disorders that are routinely included are autistic disorder or classic autism, Asperger Syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS).
Autism is differentiated from Asperger Syndrome primarily by a lack of cognitive or language delay in developmental history while atypical presentations of autism, due to late onset or presentation of atypical or sub-threshold autistic symptomology is classified under PDD-NOS (DSM-IV-TR, APA 2000).

While each individual diagnosed with ASD may present differently, there are three symptoms that constitute the diagnostic criteria for ASD: restricted and repetitive behaviour or interests, impairments in communication and impairments in social interaction. Restricted interests are characterized by circumscribed interests or preoccupation with particular activities while repetitive behaviour encompasses recurring and unusual bodily mannerisms such as stimming, a term that describes a repetitive body movement from which the individual derives sensory stimulation (i.e., hand flapping) or behaviours that have established and fixed patterns. Deficits in communication include failure to acquire speech without intervention, abnormal intonations, echolalia, and impairments in engaging in conversation. Lastly, social impairments encompass poor eye contact, difficulties in forming interpersonal relationships, deriving and reciprocating emotions in interpersonal interactions, and, the crux of the current study, understanding emotions as seen in other’s facial expressions.

With a ten-fold increase in prevalence rates of ASD from the 1960s to today, research into the heterogeneous nature of this disorder has burgeoned. Although past studies have suggested a strong genetic link to ASD (i.e., Bailey et al., 1995), Hallmayer and colleagues (2011) recently suggested that genetics instead play a moderate role, substantially less than the 90% cited in previous studies, in aggregation with environmental factors. Nevertheless, the search for a biomarker for ASD persists.

1.3 Typical development of emotional face processing

Early facial emotion discrimination between happy, sad and surprised faces in neonates, as early as 36 hours after birth, has been reported (Field et al., 1982), and categorizing emotions has also been observed in infancy (Labarbera, Izard, Vietze, & Parisi, 1976). However, despite early and intense exposure to emotional faces, recognition of emotional face expressions follows a protracted development trajectory that extends well into late adolescence (e.g., Kolb et al.,
1992; Batty & Taylor, 2006). While the ability to perceive basic emotions is largely in place by six years of age, accuracy in discriminating between facial expressions as well as recognition of more complex emotions appears to be concomitant with age (De Sonneville et al., 2002; Kolb et al., 1992; Markham & Adams, 1992; Tottenham, Hare, & Casey, 2011; Tremblay, Kirouac & Dore, 2001). Maturation of emotional processing for unique emotions is staggered across development, with the ability to accurately identify happy expressions maturing earliest while accurate identification of negative emotions such as anger and fear mature at later ages, suggesting that negative emotions require more complex processing (Markham & Adams, 1992). Evidence that different emotions follow distinct developmental trajectories was further found in reports of a significant increase in sensitivity towards anger from adolescence to adulthood, in contrast to fear, which increased linearly from late childhood to adulthood (Thomas, De Bellis, Graham, & LabBar, 2007). A developmental phase at around 11 years of age during which emotional processing abilities undergo marked improvement has been found, suggesting greater demands on neural areas implicated in emotional processing in early adolescence (Tonks Williams, Frampton, Yates, & Slater, 2007).

1.4 Emotional face processing in ASD

While it is generally understood that individuals with ASD experience difficulties with social cues, current literature on emotional face processing in ASD has been equivocal. Adults with high functioning autism have been found to make abnormal use of facial features, attending primarily on mouth rather than eye regions, when processing faces (Spezio, Adolphs, Hurley, & Piven, 2007). Hence, abnormal emotional facial processing would not be surprising. While impairments have been identified (e.g., Celani et al. 1999; Garcia-Villamisar, Rojahn, Zaja & Jodra, 2010; Golan et al. 2008; Mazefsky and Oswald 2008), with specific impairment in fear (Ashwin et al., 2007; Howard et al. 2000; Pelphery, Sasson, Reznick, Paul, Goldman, & Piven, 2002), surprise (Baron-Cohen, Spitz, & Cross, 1993) and anger processing (Teunisse & de Gelder, 2001), others have found no such evidence (e.g., Adolphs et al. 2001; Balconi & Carrera, 2007; Buitelaar et al., 1999; Castelli 2005; Tracy, Robins, Schriber, & Solomon, 2011). Furthermore, an enormous gap exists in the current literature: most past studies have neglected to consider the adolescent period in individuals with ASD.
Inconsistencies within the present literature may be due to several possibilities. Selection of emotional facial expressions, task demands, dynamic versus static expressions, participant sample specificities (i.e. narrow versus broad age ranges, inclusion versus exclusion of comorbidities, high functioning versus low functioning individuals, etc.) may all play a role in determining whether or not impairments in emotional face processing were observed in individuals with ASD (see Bal et al., 2010; Harms, Martin, & Wallace, 2010 for reviews). Since standardizing emotional face processing tasks and participant samples is impractical, there is a need to fill the gaps in the existing literature. The present work attempts to do so by focusing on a seldom studied age group, investigating emotional processing of an infrequently used threat-stimulus, angry faces, and supplementing behavioural results with neural timing and spatial information of the underlying processing of angry and happy faces.

It remains undetermined whether individuals with ASD circumvent impairment in emotional processing by effectively utilizing compensatory strategies or whether an impairment in the more complex process of assigning social significance to perceived emotions masks an intact emotional processing (Castelli, 2005). It is plausible that a deficit in theory of mind plays a role in emotion recognition impairment in individuals with ASD. In Baron-Cohen and colleague’s (1993) study, children with autism were observed to be specifically impaired in the recognition of surprise while performing comparably with happiness and sadness. This finding may be attributable to the fact that surprise is a ‘belief-based’ emotion while happiness and sadness are ‘reality-based’ expressions.

Task demands, age and cognitive level of functioning may also play important roles in the inconclusive findings in the existing literature. Studies involving perceptually oriented tasks (e.g., matching) and older higher-functioning individuals (> 12 years) tend to find comparable performance between ASD and control groups while studies requiring younger participants (younger than 10 years) to produce labels of emotional expressions produce differences in competency (see Rump et al., 2009 for a review). Collectively, these results suggest a need to examine the adolescent period of emotional processing in autism to derive a clearer understanding of the underlying developmental mechanisms in both typical and ASD populations.
The reports of equivalent proficiency of high-functioning individuals with autism, from adolescence to adulthood, relative to typically developing individuals on tasks of emotion recognition are tenuous, as comparable performance disappears with brief or subtle presentations of emotional stimuli (Grossman, Klin, Carter, & Volkmar, 2000; Humphreys, Minshew, Leonard, & Behrmann, 2007; Mazefsky & Oswald, 2007). Furthermore, while emotional face recognition in ASD was found to be significantly impaired in childhood, this impairment was observed again only in adulthood, with no deficits observed in adolescence (Rump et al., 2009). Impairment in emotional processing in adults with ASD is consistent with the notion that while compensatory strategies may be utilized by individuals with ASD and competency with emotional recognition in individuals with ASD has been found to improve with age, adults with autism still experience difficulties when presented with brief or subtle emotions, and may never reach the same level of competency in emotional processing as typically developing individuals (Kuusikko et al., 2009; Teunisse & de Gelder, 2001).

1.5 Anger processing in ASD

Accurate perception of threat-relevant stimuli in the environment contributes to survival by preparing the individual for adaptive action. While emotional facial expressions of fear and anger both constitute threat-relevant signals, the present study utilizes angry faces, which is more relevant to emotional research in the ASD population. Much of the existing emotional face processing literature has been conducted using fear as a threat-relevant stimulus leaving a relative dearth of studies that use anger.

The presentation of angry faces as threat-relevant stimuli is more appropriate for investigating emotional face processing in ASD as anger is a self-conscious emotion and social norms and context, with which individuals with ASD markedly struggle, influences the expression of anger (Berkowitz, 1999; Zeman & Garber, 1996). Furthermore, angry facial expressions are more likely to be produced in response to repeated aggravations rather than first-time behavioural transgressions (Averill, 1982). Given that individuals with ASD have been found to be incognizant of other’s mental states or of social norms, individuals with ASD have
likely encountered displays of anger without understanding the implications (Baron-Cohen, O’Riordan, Stone, Jones, & Plaisted, 1999; Begeer, Rieffe, Terwogt, & Stockmann, 2006).

Deficits in angry facial processing in individuals with ASD have been observed. When asked to describe experiences of single emotions (sadness, happiness, fear and anger), children with autism were specifically less likely to acknowledge feeling anger (Rieffe, Terwogt, & Kotronopoulou, 2007). Impairment in anger processing in ASD has been supported in a finding that while children with ASD as a group scored significantly poorer on a task of emotion recognition with brief and dynamic stimuli across a variety of emotions (including happy, sad, angry, and afraid) relative to controls, significant between-group differences were seen on only angry and fearful presentations (Rump, Giovannelli, Minshew & Strauss, 2009). Kuusikko et al. (2009) also reported that individuals with ASD were found to be significantly more impaired in anger recognition relative to controls. Furthermore, the same study found that individuals with ASD more frequently misidentified ambiguous (neutral) facial expressions as anger (Kuusikko et al., 2009). Children with ASD, when shown happy, surprised, angry and sad facial expressions, were impaired specifically on anger recognition even after controlling for IQ and age, in addition to showing longer response latencies to recognize emotions overall (Bal et al., 2010). The same study also found correlations between communicative and social responsiveness abilities to errors in anger recognition, suggesting that children with ASD require contextual cues when interpreting angry facial expressions (Bal et al., 2010).

Impairment in anger processing in individuals with ASD may thus lie in its conceptualization. That is, unlike fear, in which threat is ambiguous in source, anger embodies threat in its more directed form; it signals that an act of transgression was committed. Thus anger is expressed in order to instigate behavioural extinction or response reversal from the target individual (Blair et al., 1999). Thus, while facial expressions of fear can be conceived of as contextual cues, expressions of anger can be characterized as specific cues (Whalen et al., 1998). This notion is in concordance with an fMRI study contrasting activations elicited by fear and anger in typical individuals, which showed that while fear and anger similarly activated a network of regions including the amygdala and insula, anger specifically elicited neural activation in a wider set of additional regions including the ventromedial prefrontal cortex and
the posterior region of the orbitofrontal cortex (Pichon, de Gelder, & Grèzes, 2009). That these areas have been implicated in behavioural regulation supports the idea that anger processing requires more resources and contextual information in order to adjust behaviour accordingly (Pichon, de Gelder, & Grèzes, 2008). While age-related improvements in implicit processing of anger been noted in childhood and early adolescence, sensitivity to anger has been shown to increase sharply from adolescence to adulthood, providing support for a later maturational curve for anger (Herba, Landau, Russell, Ecker & Phillips, 2006; Thomas, De Bellis, Graham, & LaBar, 2007).

Collectively, the findings of these studies converge upon the notion that angry facial expressions constitute a specific social cue, and that their successful perception, interpretation, and behavioural adjustment requires further contextual information, relative to fearful faces (Bal et al., 2010; Whalen et al., 1998). That the processing of angry faces denotes a lack of contextual information may be a mechanism to explain the specific impairments towards anger processing observed in individuals with ASD.

1.6 Happy processing in ASD

Happiness is the only one of the six basic emotions that is definitively positive and is accurately identified the earliest in development (Markham & Adams, 1992). In addition to being opposite in its emotional polarity to angry faces, happy faces are important visual stimuli to study in individuals with ASD as have been suggested to be socially rewarding for typically developing individuals (Phillips et al., 1998). While typical processing of happy affect in individuals with ASD has been observed, which may be due to the greater frequency of encountering and becoming familiar with happy faces for individuals with ASD (Critchley et al., 2000; Farran, Branson, & King, 2011), insensitivity towards social reward derived from happy faces has also been shown in individuals with ASD (Sepeta et al., 2012). Hence, investigating deficits in deriving social reward from happy faces may contribute towards further understanding of social impairment in individuals with ASD.
1.7 Adolescence

Adolescence encompasses much of the second decade of life and is characterized by marked physical, behavioural, cognitive and social changes as a person transitions from childhood to adulthood. It is thus not surprising that neuroanatomical changes are also occurring in the adolescent brain; the frontal lobes increase in size, grey matter peaks in early adolescence then declines, white matter volumes increase steadily throughout adolescence while subcortical structures such as the amygdalae show a marked increase in size (Giedd, Molloy, & Blumenthal, 2002; Paus, 2005).

Adolescence is often a time of vulnerability, volatility, and increased stress (Spear 2000). Amongst affective changes experienced in adolescence are a peak in prevalence of negative emotional states as well as behavioural and neuroimaging findings of heightened and more variable emotional responses (Compas, Hinden, & Gerdhard, 1995; Hare, Tottenham, Galvan, et al. 2008).

Behavioural analyses of adolescent reaction time data to emotional faces are also inconsistent. While one study found a significant effect of emotional expression on response latency, with the fastest response times for neutral faces and the slowest response times for angry faces (Monk et al., 2003), others have reported no effect of emotion on response times (Hung et al., 2012; Guyer, Monk, McClure-Tone, et al., 2008). These inconsistencies in findings of emotional processing in adolescents may be due to task differences and require further investigation.

Given that emotional face processing matures into early adolescence (Batty & Taylor, 2006; Kolb et al., 1992), whether the neural mechanisms underlying emotional face processing in adults are the same structures as those recruited during adolescence is of particular interest. Emotional face processing during adolescence may reflect immature underlying neural networks and development of functional specialization in those structures or the recruitment of a different set of neural structures, suggesting that functional specialization in emotional face processing occurs on a larger scale. Taylor, Mills, and Pang (2011) have suggested that between childhood and adulthood, maturation of face recognition processing reflects protracted development in
similar brain regions, which has implications for age-related differences in strategies and neural activation during emotional face processing. Unfortunately, while the number of behavioural studies of the development of emotional processing is not lacking, literature on the neural correlates of emotional processing has been largely focused on matured processes in the adult population and not its development.

Nevertheless, a recent study conducted by Hung et al. (2012) determined that there is indeed a shift in the neural networks recruited for emotional face processing during the course of development. They investigated implicit emotional face processing in typically developing children and adolescents using magnetoencephalography (MEG). Participants were concurrently shown a fearful or happy face with a scrambled pattern, and instructed to indicate the location of the scrambled pattern. They found a shifting involvement of neural networks implicated in emotional processing between childhood and adolescence. In contrast to children, in whom significant left amygdala activation was found regardless of emotion, in adolescents, the anterior cingulate cortex (ACC) showed significant activation towards fearful faces, whereas the right amygdala showed activation regardless of emotion. Of particular interest was that although ACC activation was observed in both adolescents and adults, greater ACC activation was found in adults. Together, these results suggest that functional specialization occurs earlier in the amygdalae, which is followed by later development in the ACC.

In two studies by Monk and colleagues (2003) and Guyer and colleagues (2008), adolescents and adults rated nose-widths of angry, fearful and happy faces during fMRI. In response to fearful faces, there was greater activation in the ACC (Monk et al., 2003) and the amygdalae in adolescents (Guyer et al., 2008) in comparison to adults. The findings of Guyer et al. (2008) are also consistent with findings of elevated neural responses to emotion in adolescence (Hare et al., 2008). Collectively, these three studies documented consistent ACC and amygdalae involvement in adolescent processing of fearful faces.
1.8 Neural substrates of typical emotional face processing

1.7.1. Source localization of typical emotional face processing

Emotional face processing has been found to be associated with greater activation in a number of areas of the brain, encompassing visual, limbic, temporal, temporoparietal, and prefrontal regions (Blair et al., 1999; Fusar-Poli et al., 2009; Phillips et al., 1999; Vuilleumier & Pourtois, 2007). The involvement of a variety of neural structures is consistent with the notion that emotional face processing is a complex process that recruits a network of different neural structures across time. The diversity of neural structures involved in emotional processing thus renders it pragmatic to focus on particular emotional expressions of interest, which, in the present study are happy and angry affect, and their neural substrates.

The processing of happy facial expressions is implicated a number of structures including the amygdala, insula, medial frontal, middle frontal, and middle temporal areas (Brauer, Brasse, Striano, & Friederici, 2010; Devinsky et al. 1995; Fusar-Poli et al., 2009; Kesler/West et al., 2001; Sprengelmeyer et al., 1998). Processing of happy facial affect has also been observed to elicit enhanced activity in the anterior cingulate, medial frontal, and posterior cingulate areas (Phillips et al., 1998). Amygdalae and fusiform activation has also been found in response to happy faces (Breiter et al., 1996; Thomas et al., 1999).

The orbitofrontal cortex has received particular interest in anger processing due to its role in mediating emotional behaviour, social inhibition, reversal learning, and altering of unsuitable behaviour (Blair, Morris, Frith, Perrett, & Dolan, 1999; Dias et al., 1996; Elliot, Dolan, & Frith, 2000; van Hon et al., 2005). Findings of greater orbitofrontal activity in response to anger suggest its implication in sensitivity to social disapproval, for which anger is a cue (Blair, Morris, Frith, Perrett, & Dolan; 1999; Jollant et al., 2008).

Angry faces have also been observed to elicit cingulate, bilateral fusiform, inferior frontal, superior temporal, and middle and medial superior frontal activations (Blair et al., 1999; Devinsky et al. 1995; Fusar-Poli et al., 2009; Kesler/West et al., 2001; Sprengelmeyer et al., 1998). Furthermore, increasing anger intensity elicited enhanced activity in the orbitofrontal and
anterior cingulate cortex (e.g., Blair et al., 1999). Interestingly, hypoactivation to angry, relative to neutral faces, has also been observed in the superior temporal gyrus, anterior cingulate gyrus, medial frontal gyrus and caudate nucleus (Phillips et al., 1999). While the amygdalae have been widely reported to be involved in threat processing, amygdalae activity towards angry faces has been controversial. While angry faces have been found by some to elicit amygdalae activity (e.g., Luo, Holroyd, Jones, Hendler, & Blair, 2007; Phillips et al., 1999; Whalen et al., 2001), others have found no amygdalae activity (e.g., Fusar-Poli et al., 2009).

Neural mechanisms underlying the ability to perceive and interpret emotional expression develop throughout childhood and are immature even by early adolescence (Batty & Taylor, 2006). The staggered development of emotional processing seen in behavioural data suggests the recruitment of different neural structures during emotional face processing over the course of development (Markham & Adams, 1992). While findings of similar regions of activation in children and adults during implicit emotional processing have been reported (Lobaugh, Gibson, & Taylor, 2006; Brauer, Brasse, Striano, & Friederici, 2010), other studies have also documented greater recruitment of visual and limbic areas in young adults in comparison to the recruitment of parietal, temporal and frontal areas found in older adults (Gunning-Dixon, Gur, Perkins, et al., 2003). Children have also been found to have greater amygdalae activation during emotional processing, relative to adults (Brauer, Brasse, Striano, & Friederici, 2010). These findings suggest that functional specialization may be an ongoing process that does not stop but continues developing following maturation at young adulthood, underlining the need for adolescent studies.

1.7.2. Temporal profile of neural activation during typical emotional face processing

The majority of studies investigating facial expression processing have been conducted with neuroimaging techniques that have allowed for spatial mapping of this process. Due to the complex nature of emotional face processing, however, there is a need for studies examining the temporal dynamic underlying emotional face processing (Vuilleumier & Pourtois, 2007). Evidence of differences in temporal dynamics in processing facial affect has been documented in
previous studies as well as early (80-90 ms) neural activation sensitive to emotional content (Batty & Taylor, 2003; Eger, Jedynak, Iwaki, & Skrandies, 2003; Halgren, Raij, Marinkovic, Jousmäki, & Hari, 2000; Münte et al., 1998). Age-related changes in neural activation underlying emotional face processing has also been observed in an ERP study by Batty and Taylor (2006), which showed emotion affecting amplitude of N170 in adults and older (14-15 years of age) but not younger children. In adults with ASD, delayed and smaller N170 components were found across all facial expressions (including neutral); this difference was not observed in children with ASD, which is inconsistent with previous studies (O’Connor Hamm, & Kirk, 2005).

Of particular relevance to the present research, a previous study conducted by Luo and colleagues (2007) examined angry face processing using MEG. They documented early occipitotemporal activation in response to angry faces (20-30 ms, peaking around 140-150 ms) and late left amygdala activity (150-160ms, peaking at 210-220 ms and offsetting at 260-270 ms). Late orbitofrontal activity towards angry faces was also observed (onset at 170-180 ms, peaking around 200-210 ms, and offset at 230-240 ms). Lastly, they also noted a temporal profile for right anterior cingulate cortical activity (170-180 ms, peaked at 220-230 ms, and offset at 270-280 ms).

1.8 Neural substrates of emotional face processing in ASD

1.8.1. Source localization of emotional face processing in ASD

Deficits in emotional face processing in ASD have been suggested to be due to the fact that emotional faces are not emotionally stimulating for individuals with ASD and thus they do not preferentially attend to them (Schultz, 2005). The suggestion that faces lack emotional salience in ASD is consistent with neuroimaging findings that, when looking at faces, individuals with ASD exhibit neural activity akin to controls looking at objects (Schultz, Gauthier, Klin, et al., 2000).

Using fMRI, Ashwin et al. (2007) investigated fearful face processing in adults with Asperger Syndrome or high functioning autism and found distinct activation of the social brain in individuals with ASD relative to controls. While the ASD group exhibited reduced left
amygdala and left orbitofrontal cortex activation, they showed no effect of fear intensity on the social brain network in the ASD group, in contrast to the control group. In a group comparison, they also found greater anterior cingulate cortex activation in individuals with ASD. Their findings suggest different facial processing strategies between individuals with and without ASD. Discrepant activation towards emotional faces in individuals with ASD using fMRI was also shown by Deeley and colleagues (2007), who found that while adults with Asperger syndrome and controls both showed activation in face perception areas, including anterior cingulate, superior temporal, medial frontal, and insula activation, adults with Asperger syndrome also showed reduced fusiform and extrastriate activation, relative to controls. Neither group exhibited amygdala activation, which is consistent with Baron-Cohen and colleagues’ (1999) findings for adults with ASD, Sprengelmeyer and colleagues’ (1998) findings in controls, and Baron-Cohen and colleagues’ amygdala theory of autism. However, Deeley and colleagues (2007) suggested that deficits in the limbic network feedback as a whole may account for differences in activation, rather than amygdalae abnormality being the sole cause.

Individuals with ASD have shown activation to emotional faces in the left superior and middle temporal gyrus, left anterior insula, as well as the left dorsolateral prefrontal cortex (Critchley et al., 2000). Significant group differences were noted: participants with autism showed significantly greater activity in the left superior temporal gyrus and right peristriate visual cortex, relative to controls (Critchley et al., 2000). More recently, children and adolescents with ASD showed less fusiform but more precuneus activity during an emotion-matching task (Wang et al., 2004). Furthermore, there were no group differences during a simpler emotion labeling task, suggesting that task demands modulate neural activation during emotional processing in individuals with ASD and may account for discrepant findings in the current literature (Wang et al., 2004).

1.8.2. Temporal profile of neural activation during emotional face processing in ASD

While neuroimaging techniques such as fMRI yield excellent spatial resolution in determining where neural activity occurs during emotional face processing in ASD, they do not
produce any information regarding the temporal properties of the neural activation, which is important given the complex nature of emotional face processing. Recently, studies using techniques with high temporal resolution have sought to fill in this gap in the current literature and have found atypical temporal activation in individuals with ASD. Findings of delay in a face-sensitive early ERP component (N170) in bilateral temporal regions in individuals with ASD, relative to controls, suggest that aberrant emotional face processing in ASD may be attributable to initial atypical face processing (McPartland, Dawson, Webb, Panagiotides, & Carver, 2004).

Atypical emotional face processing has been found in children with ASD as young as three to four years of age in an ERP study. While young typically developing controls have been observed to show a large early negative component to fearful, relative to neutral, faces, children with ASD did not show enhanced activation in response to the fearful faces (Dawson, Webb, Carver, Panagiotides, & McPartland, 2004). The same study also found early fear processing was associated with better performance on social tasks, underlining the intrinsic relation between emotional face processing and social aptitude. Further support for atypical neural activation in children with high functioning ASD was found in a study conducted by Wong and colleagues (2008). Despite comparable behavioural performance, decreased and delayed ERP responses in the visual cortex, fusiform gyrus, and medial prefrontal regions, areas implicated in face and emotional state processing, were observed during explicit and implicit emotional processing tasks (Wong, Fung, Chua, & McAlonan, 2008). Findings of atypical activation in children with ASD have been more recently confirmed where ERP responses to faces were found to be delayed and smaller in children with autism (Batty, Meaux, Wittemeyer, Rogé, & Taylor, 2011).

In summary, the current literature converges upon an atypical spatiotemporal profile of neural activation during emotional face processing in ASD. Examination of current literature further highlights a need for research studies using neuroimaging techniques with high temporal resolution to investigate emotional face processing, a complex process that implicates a wide array of neural structures across time, in ASD.
Chapter 2
Objectives and Hypothesis

Emotional human faces are one of the most important and salient visual emotional stimuli that humans encounter and the ability to perceive and recognize emotional faces are integral to social interactions. Given that impairments in social interaction and communication are diagnostic indices of ASD, impairments in emotional face processing in individuals with ASD are not surprising, yet our understanding of the development and neural underpinnings is yet still rudimentary.

Behavioural and neuroimaging findings of emotional face processing frequently yield inconsistent results, underlining the importance for further research into this field. The literature on emotional face processing has been dominated by emotional processing in typical adults, while the neural mechanisms underlying typical development of emotional face processing is less clear. Investigating the neural substrates of emotional processing in adolescence, a critical developmental period between rudimentary processing and maturity, will allow us to add to the literature on affective changes during adolescence, and to further our understanding of the neural changes that underlie cognitive affective mechanisms during this critical period. This study is also unique in its use of angry faces as threat-relevant stimuli. Angry faces, in addition to being infrequently used as threat stimuli, are more appropriate for investigating emotional face processing and social cognition in ASD as anger processing involves implications of social norms and context, with which individuals with ASD have difficulty (Berkowitz, 1999; Zeman & Garber, 1996). Hence, the objective of the present study is to examine the temporal and spatial properties of neural activity during angry and happy processing in adolescents with and without ASD through the use of MEG, as well as its cognitive and behavioural correlates.

To the best of our knowledge, this is the first study to explore the neural substrates of emotional face processing in adolescents with autism using magnetoencephalography, yielding insight into both the temporal as well as spatial properties of these processes. We hypothesize that adolescents with autism will exhibit reduced patterns of neural activation, particularly
towards angry faces, in areas of the social brain such as the superior temporal sulcus and the orbitofrontal cortex.
Chapter 3
Methods

3.1 Participants

Thirteen adolescents with ASD (high functioning autism and Asperger Syndrome; $M = 14.44$ years, $SD = 1.19$, 12 males) and 14 age- and sex-matched controls ($M = 14.36$ years, $SD = 1.18$, 13 males) were recruited. All participants were right-handed. Exclusion criteria for both groups included a history of neurological or development disorders (other than ASD for participants in the clinical group), prematurity, uncorrected vision, colour blindness, IQ lower than 65, language skills inadequate for completion of the tasks, and standard contraindications to MEG and MRI. In addition, the use of psychotropic medications was also used as a factor for exclusion for control participants only, due to difficulty in recruiting medication-naïve individuals with ASD. Three participants in the ASD group were on medication. Typically developing adolescents were recruited via word of mouth, posters, as well as fliers at the Hospital for Sick Children. Adolescents with ASD were recruited through fliers at the Hospital for Sick Children, the lab database, and online fliers on the Geneva Centre for Autism website as well as the Centre’s monthly newsletter postings. The study protocol was approved by The Hospital for Sick Children research ethics board and written informed consent was obtained from participants and from parents of those younger than 16 years of age.

3.2 Measures of Autistic Symptomatology

The clinical diagnosis of ASD was confirmed with the "Autism Diagnostic Observation Schedule - General (ADOS-G; Lord, Rutter, DiLavore, Risi, et al., 2000). The ADOS-G is a semi-structured standardized assessment for individuals who are suspected to be on the autism spectrum. The ADOS-G is comprised of four modules; for the current study only Modules 3 and 4 were used, as they are most suitable for individuals who possess fluent speech. The difference between Modules 3 and 4 is that Module 3 is appropriate for children or adolescents who are still interested in playing with toys (i.e., action figures) while Module 4 is for adolescents or adults for whom playing with toys is inappropriate. Administration of the ADOS-G takes
approximately one hour. The ADOS generates three scores consisting of communication, social interaction, and a summary score from summing the communication and social interaction subscale score in order to determine whether each of the three scores reach cut-offs suggesting a potential diagnosis of autism or autism spectrum disorders.

### 3.3 Behavioural Assessments

Parents of all participants were asked to complete four behavioural response forms (Conners’ ADHD/DSM-IV Scales, Behavior Rating Inventory of Executive Function, Repetitive Behavior Scale-Revised and the Social Responsiveness Scale) prior to or during their child’s first session.

The *Conners’ ADHD/DSM-IV Scales (CADS; Conners, 1997)* is a brief informant-based report for children and adolescents aged 3-17 years with 26 items to screen for children at risk for attention deficit hyperactivity disorder (ADHD).

The *Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, et al., 2000)* is a parental response form that assesses difficulties with every day executive function in the home environment in children and adolescents aged five to 18 years with a range of developmental and neurological conditions. This assessment has high internal consistency (alphas = .80 - .98), high test-retest reliability ($r_s = .82$ for parents), as well as convergent validity with other measures of executive function.

The *Repetitive Behavior Scale-Revised (RBS-R; Bodfish, Symons, & Lewis, 1999)* assesses repetitive behaviour in autism based on an informant (in this case, the parent). The items on the RBS-R are grouped into five subscales: stereotypic behaviour, self-injurious, compulsive, ritualistic or sameness behaviour, and restricted interests. Studies have found high internal consistency and inter-rater reliability data for the RBS-R (Lam & Aman, 2007).

The *Social Responsiveness Scale (SRS; Constantino & Gruber, 2005)* is a 65 item informant-based report designed to distinguish autism spectrum symptoms from other child psychiatric symptoms in children and adolescents aged four to 18 years. Domains explored by
the SRS include a child’s social impairments, assessing social awareness, social information processing, capacity for reciprocal social communication, social anxiety or avoidance and autistic preoccupations and traits. The SRS measures social impairment on a 4-point scale (1=not true, 4=almost always true) in order to identify the presence and extent of autistic social impairment.

3.4 Tasks and Procedures

Participants completed cognitive tasks assessing IQ, affect recognition, and executive function outside of the scanner, as well as an emotional face processing task in the MEG scanner. The duration of the testing was approximately three hours. Breaks were given to participants depending on scheduling (i.e., if they were scheduled to complete all portions of the study in one day they would receive a lunch break and breaks between neuroimaging sessions) to maintain motivation.

3.4.1 Cognitive assessments

The *Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2002)* is a standardized measure of intelligence for individuals six to 89 years of age. The shorter two-subtest version, comprised of the Vocabulary and Matrix Reasoning subtests, was administered to provide a measure of general IQ. The Vocabulary subtest includes 38 items that measure word knowledge, verbal concept formation and knowledge. The *Matrix Reasoning* subtest consists of 35 items and is used for measuring visual information processing and abstract reasoning skill.

The *Developmental Neuropsychological Assessment, Second Edition (NEPSY-II; Korkman, Kirk, & Kemp, 2007)* assesses six domains (executive function and attention, language, learning and memory, sensorimotor, visuospatial processing, and social perception) in children aged three to 16 years and possesses convergent validity with other tests such as the Weschler Intelligence Scale for Children (WISC-IV; Wechsler, 2003) and the Delis-Kaplan Executive Function System (DKEFS; Delis, Kaplan, Kramer, & Ober, 1997). The NEPSY-II is advantageous in that it is designed to assess specific domains independently. We administered subtests in the social perception (affect recognition), executive functioning and attention domains
(animal sorting, inhibition) to all participants. The Affect Recognition subtest assesses participants’ ability to recognize affect (happy sad, neutral, fear, angry, and disgust) by asking participants to select photographs that show children with the same affect as a target photograph of a child. This subtest also assesses memory for affect as participants are briefly shown a photograph and then are asked to select two photographs from memory that show the same affect as the target photograph. The Animal Sorting subtest is a measure of participant’s ability to generate basic concepts (i.e., size, colour) upon viewing a number of cards that can be sorted in different ways, carry out actions based on those rudimentary concepts by taking the initiative to sort those cards into groups, and lastly, cognitive flexibility by being able to switch between different concepts for sorting. Finally, the Inhibition subtest measures the ability to inhibit responses that are automatic responses (e.g., asked to say ‘square’ instead of circle when shown a circle) as well as cognitive flexibility by being able to switch between different responses (e.g., when the shape is black, say the shape’s correct name, when the shape is white, say the other shape’s name).

3.5 MEG Emotional Face Task

3.5.1 Stimuli

Emotional face stimuli were taken from NimStim set of faces (Tottenham et al., 2009) and consisted of twenty-five happy, neutral and angry faces (13 females and 12 males for each expression). Faces in the NimStim set are given with validity ratings and only happy and angry faces with more than 80% validity were chosen.

To create a corresponding scrambled pattern (target), a face from the NimStim set was scrambled by first dividing each unique face into 32 tiles (4x8), which were then manually shuffled so that they appeared, randomised. After shuffling, the entire image was further divided into four columns (for a total of 64 unique tiles), which again were shuffled randomly. Following this, images were then mosaicked (15 cells per square) after which Gaussian blur was applied (10.0 degrees). Finally, images were controlled for luminosity and colour such that there were no
differences in those two properties amongst scrambled pattern-face pairs. Stimuli were presented using Presentation software (http://www.neurobs.com/).

3.5.2 Procedure

Emotional faces and corresponding scrambled patterns were concurrently presented on either side of a white central fixation cross on a black-background screen. Images were back-projected through a set of mirrors onto a screen positioned at a viewing distance of 79 cm. The adolescents underwent practice trials prior to the start of the task to ensure proficiency at and understanding of the task. Participants were instructed to fixate on the central cross while responding as quickly as possible to indicate the location of the scrambled pattern (the target) by pressing the left or right button on a response button box. The stimuli in each trial were presented for 80 ms to avoid saccadic movement with an ISI varying from 1300 to 1500ms. Fifty trials of each of the three emotions in the left and right hemifields (each unique face is shown twice in each hemifield) were shown so that the task in total included 300 trials. Twenty-five different emotional faces were randomly presented for each expression (a total of 75 faces were used). The visual angle of the stimuli was 6.9° and fell within the parafoveal region of view.

3.6 MEG Data Acquisition

Neuromagnetic data were recorded using a 151-channel CTF MEG system (CTF Systems Inc., Port Coquitlam, BC, Canada) at 600 Hz sampling rate in a magnetically shielded room at the Hospital for Sick Children. A third order software spatial gradient was used to facilitate noise removal (Vrba, Anderson, Betts, et al., 1999) with a recording band pass of 0-150 Hz. Data were time-locked to trial onset. All participants lay in a supine position with their head in the MEG dewar while they completed the experimental paradigm. Head coils were placed on the left and right pre-auricular points and the nasion to determine head position relative to MEG sensors as well as to co-register each participant’s MEG data with their MRI anatomical scan. Participants were asked to remain as still as possible during scanning. Continual head localization tracked amount of head movement. Duration of data collection was approximately 7 minutes.
3.7 MEG Data Processing

MEG data were epoched into trials of 650ms (from -150 ms to 500 ms relative to stimulus onset), sorted by emotion and filtered off-line with a bandpass of 1 to 30 Hz. Using DataEditor software, trials with artefacts (i.e., eyeblinks) as well as those on which head movement exceeded 10 mm (relative initial head position) were manually excluded.

3.8 Anatomical MRI Acquisition

Whole brain anatomical scans were acquired from each participant on a 3T MR scanner (MAGNETOM Tim Trio, Siemens AG, Erlangen, Germany), with a 12-channel head coil. T1-contrast anatomical scans were obtained using a 3D SAG MPRAGE sequence: PAT, GRAPPA=2, FA = 9°, TR/TE = 2300/2.96 ms, FOV = 28.8x19.2cm, 256x256 matrix, 192 slices, slice thickness = 1.0 mm isotropic voxels, scan time = 5:03 min.

3.9 Anatomical MRI Processing and Co-registration

Each participant’s anatomical MRI data were converted into CTF compatible data using CTF programs MRIConverter and MRIViewer (CTF MEG™ Software, VSM MedTech Ltd.). Multisphere headmodels were created according to fiducial positions marked during MEG data acquisition. Anatomical images were normalized to a template using SPM2 (Statistical Parametric Mapping, version 2, http://www.fil.ion.ucl.ac.uk/spm/software/spm2).

3.10 Behavioural Analyses

Response latencies, defined as time of stimulus onset until participant response, were analyzed in a 2x2 MANOVA (two participant groups: ASD versus controls, 2 levels of emotion contrasts: happy, angry) with SPSS 19.0 software package (SPSS, Inc., Chicago, IL, USA). To determine group differences in behaviour, four MANOVAs were conducted on individual subscales in each parental response form (BRIEF, CADS, RBS-R, and SRS). Multiple comparisons were corrected using the Bonferroni method.
3.11 MEG Analyses

Grand average datasets were created for each condition by first averaging across all trials for each emotion for each participant (i.e., all happy trials for participant 1) then in turn averaging these average datasets across all participants. Global field power plots (GFPs; root mean squared power across all sensors) were generated for grand-averaged datasets in each condition and depict the strength of the magnetic field as measured by the MEG. We examined the between group differences in each valenced emotion-neutral contrast with the neutral condition as a baseline, but due to comparable peak latencies seen in the GFP plots between the valenced emotions and neutral conditions, we chose to examine neural activity in angry and happy conditions without first contrasting them with the neutral condition.

Emotion-related activation sources for each subject and emotion were estimated using an event-related beamforming (ERB) method (Cheyne et al., 2007; Quran et al., 2010) developed in-house. ERB is an adaptive spatial filtering technique that is able to overcome artefact issues such as those due to movement in the eyes. ERB analyses were performed from 80 ms to 280 ms, divided into five non-overlapping time windows spanning 40 ms each (e.g., 80-120 ms, 120-160 ms).

Mri3dX (http://cubric.psych.cf.ac.uk/Documentation/mri3dX) was used to view regions of activation to guide statistical analyses within groups. Peak activations were selected and their Talairach coordinates were input into TalairachClient to confirm regions of interest (Lancaster, Woldorff, Parsons, Liotti, Freitas, et al., 2000; Lancaster, Rainey, Summerlin, Freitas, Fox, et al., 1997).

To determine significant within-group activity, one-sample non-parametric two-tailed permutation tests were conducted on individual ERB images (2048 permutations) for each emotion for each group.

Between-group differences in neural activation were examined by contrasting the ERB images between the two groups. Images of each emotion (either happy or angry) in the ASD group were subtracted from the corresponding subtracted images in the control group. Two-
tailed unpaired non-parametric permutation tests (5000 permutations, threshold = $p < .05$, uncorrected) were then performed on these images in each time window. Finally, MRICron software (Rorden & Brett, 2000) was then used to create 3D renderings of between group activations on spatially normalized images onto a template. Lastly, within group analyses were compared to significant contrasts, to clarify the within-group activations driving the significant between group differences.
Chapter 4
Results

4.1 Behavioural assessment results

All adolescents with ASD met ADOS cutoff for autism spectrum disorder in all three categories (communication: $M = 3.8$, $SD = 1.9$; social interaction: $M = 7.6$, $SD = 3.2$; communication and social interaction total: $M = 11.4$, $SD = 3.1$).

Adolescents with ASD showed significantly lower two-subtest FSIQ scores ($n = 13$, $M = 95.15$, $SD = .16.48$) relative to typically developing controls ($n = 14$, $M = 112.0$, $SD = 11.88$), $t(25) = 3.06$, $p = .005$. This group difference led to IQ being included in all subsequent behavioural analyses as a covariate. Four ANCOVAs were conducted for each parental form total score to investigate whether group differences existed, holding IQ constant. As all were significant, four MANCOVAs were subsequently independently conducted for each parental response form to investigate individual scales on each form, each with IQ as a covariate and corrected using the Bonferonni method. Adolescents with ASD showed significantly higher scores in the BRIEF subscales (Inhibit, Shift, Emotional Control, and Working Memory) as well as the Behavioural Regulation Index, Metacognition Index, and the Global Executive Composite (GEC), indicating deficits in these specific aspects of, and overall, executive function (see table 1: BRIEF). The GEC scores of seven of 13 (54%) participants in the ASD group met clinical significance (defined as having a T-score at or above 65) while this was true for only one individual in the control sample. In individual subscales, 38.5% individuals with ASD met clinical significance for the inhibition subscale relative to 7.1% in the control group. In the shift subscale, 76.9% of the ASD cohort met clinical significance relative to 14% of participants in the control group. For the emotional control, organization of materials and monitoring subscales, 46.1%, 7.7% and 46.1% of participants in the ASD group met clinical significance, respectively, while none of the control participants met criteria. Lastly, for the initiate, working memory and planning and organization subscales, 38.5%, 46.1% and 15.4% of participants with ASD met criteria, respectively, while only 21.4% of control participants met clinical significance for the
initiate subscale and 7.1% of control participants met clinical significance for each of the latter two scales.

Significant differences between adolescents with ASD and typically developing adolescents in the ADHD DSM-IV total score showed that adolescents with ASD included a higher number with ADHD symptomology. While no participants in the ASD group met criteria suggestive of ADHD diagnosis, one participant in the control group did met criteria suggestive of ADHD predominantly inattentive-type diagnosis, although the participant did not have any formal diagnosis (see table 2: CADS).

Parents of adolescents with ASD also reported a greater frequency of and more problematic repetitive, purposeless movements (stereotyped behaviour), repetitive actions that cause self injury (self-injurious behaviour), repetitive actions that were performed according to some rule or done ‘just so’ (compulsive behaviour), carrying out daily living activities in a similar fashion (ritualistic behaviour), and restricted behaviour than was reported for the control group (see table 1: RBS-R).

Significant differences between adolescents with ASD and typically developing adolescents on the scores of all subscales and the total score of the SRS indicate significant social impairment in the adolescents with ASD relative to controls (see table 1: SRS).

Lastly, adolescents with ASD showed significantly poorer performance ($M = 8.6$, $SD = 1.51$) on the NEPSY Affect Recognition subtest relative to controls ($M = 10.08$, $SD = 1.66$), $t(20.34) = 2.23, p = .037$. However, once IQ was accounted for, this difference in performance was no longer significant, $F(1, 20) = 2.61, p = .122$. 
### Table 1.

*Scores of Adolescents with ASD (N=13) and Control Adolescents (N=14) on BRIEF, CADS, RBS-R, and SRS Parent Response Forms*

<table>
<thead>
<tr>
<th>Parental Response Form</th>
<th>ASD</th>
<th>Control</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>BRIEF Global Executive Composite</td>
<td>12</td>
<td>65.17</td>
<td>10.77</td>
<td>13</td>
</tr>
<tr>
<td>Behavioural Regulation Index</td>
<td>66.92</td>
<td>12.76</td>
<td>46.46</td>
<td>8.57</td>
</tr>
<tr>
<td>Metacognition Index</td>
<td>91.08</td>
<td>15.51</td>
<td>72.54</td>
<td>17.66</td>
</tr>
<tr>
<td>Inhibit</td>
<td>62.00</td>
<td>13.53</td>
<td>47.23</td>
<td>8.77</td>
</tr>
<tr>
<td>Shift</td>
<td>70.67</td>
<td>13.32</td>
<td>49.54</td>
<td>11.96</td>
</tr>
<tr>
<td>Emotional Control</td>
<td>62.42</td>
<td>10.17</td>
<td>41.15</td>
<td>14.26</td>
</tr>
<tr>
<td>Initiate</td>
<td>63.75</td>
<td>9.09</td>
<td>53.00</td>
<td>13.30</td>
</tr>
<tr>
<td>Working Memory</td>
<td>64.75</td>
<td>9.50</td>
<td>51.08</td>
<td>9.17</td>
</tr>
<tr>
<td>Plan/Organize</td>
<td>59.75</td>
<td>8.77</td>
<td>50.62</td>
<td>9.96</td>
</tr>
<tr>
<td>Organization of Materials</td>
<td>53.08</td>
<td>9.65</td>
<td>51.08</td>
<td>9.26</td>
</tr>
<tr>
<td>Monitor</td>
<td>62.75</td>
<td>10.64</td>
<td>51.08</td>
<td>7.82</td>
</tr>
<tr>
<td>ADHD Index</td>
<td>10</td>
<td>62.30</td>
<td>8.27</td>
<td>14</td>
</tr>
<tr>
<td>CADS DSM-IV Total</td>
<td>62.90</td>
<td>10.48</td>
<td>50.93</td>
<td>10.01</td>
</tr>
<tr>
<td>RBS-R Overall Score</td>
<td>11</td>
<td>12.64</td>
<td>9.93</td>
<td>14</td>
</tr>
<tr>
<td>Stereotyped Behaviour</td>
<td>2.36</td>
<td>2.25</td>
<td>.43</td>
<td>.94</td>
</tr>
<tr>
<td>Self-Injurious Behaviour</td>
<td>1.18</td>
<td>1.66</td>
<td>.07</td>
<td>.27</td>
</tr>
<tr>
<td>Compulsive Behaviour</td>
<td>2.09</td>
<td>1.70</td>
<td>.21</td>
<td>.43</td>
</tr>
<tr>
<td>Ritualistic Behaviour</td>
<td>2.27</td>
<td>1.79</td>
<td>.21</td>
<td>.43</td>
</tr>
<tr>
<td>Sameness Behaviour</td>
<td>3.91</td>
<td>3.11</td>
<td>.57</td>
<td>.85</td>
</tr>
<tr>
<td>Restricted Behaviour</td>
<td>2.18</td>
<td>2.23</td>
<td>.07</td>
<td>.27</td>
</tr>
<tr>
<td>SRS Total</td>
<td>12</td>
<td>76.25</td>
<td>13.83</td>
<td>13</td>
</tr>
<tr>
<td>Social Awareness</td>
<td>68.17</td>
<td>13.36</td>
<td>42.77</td>
<td>8.47</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>72.25</td>
<td>12.97</td>
<td>40.85</td>
<td>6.44</td>
</tr>
<tr>
<td>Social Communication</td>
<td>71.92</td>
<td>13.75</td>
<td>44.08</td>
<td>9.79</td>
</tr>
<tr>
<td>Social Motivation</td>
<td>73.67</td>
<td>13.99</td>
<td>49.54</td>
<td>13.42</td>
</tr>
<tr>
<td>Autistic Mannerisms</td>
<td>75.92</td>
<td>15.19</td>
<td>44.62</td>
<td>4.99</td>
</tr>
</tbody>
</table>

*Note.* For all response forms, the higher the scores, the greater deficit in behaviour.  
* denotes a significant result after Bonferonni correction.
4.2 Emotional Face Task behavioural results

Adolescents with ASD showed shorter overall response latencies to both emotions, assessed in a 2 (emotion with 2 levels: happy and angry) X 2 (group with 2 levels: ASD and controls) MANOVA, which showed no significant group differences between response-latencies for happy and angry faces, F(1, 24) = 2.87, p = .103 (see Table 2).

Table 2.

| Response latencies of adolescents with ASD (N=13) and control adolescents (N=14) in the Emotional Face Task by condition. |
|---|---|---|---|
| | Angry | Happy |
| Group | Mean | SD | Mean | SD |
| ASD | 391.75 | 78.64 | 396.25 | 84.53 |
| Controls | 429.99 | 61.85 | 427.23 | 59.93 |

4.3 Neuroimaging results

4.3.1 Global field power plots

Global field power (GFP) plots were generated for both angry and happy conditions across both groups to guide neuroimaging analyses as shown in Figure 1a and b.
Peaks of interest first occurred at 100 ms and continued until 350 ms, establishing 80-280 ms as the time range of interest. Similarities between field power in response to neutral and other emotion conditions caused a shift in analysis approach so that each emotion was analyzed without subtracting our neural activity in response to neutral faces (see Figure 2).

Figure 1. GFP plots for angry (a) and happy (b) face conditions between groups.

Figure 2. Comparable neural activity across all emotion conditions in the ASD group.

4.3.2 Within and between group analyses of frontal activity

Within group analyses showed a number of significant areas of frontal activation in both ASD and typically developing adolescents towards angry and happy faces (see Table 3, Figure 3). Two-sample unpaired non-parametric random permutation tests ($p < .05$, uncorrected) similarly revealed a number of significant group differences in frontal activation, with more areas with significant differences activations in responses to angry than happy faces that were
larger and more diffuse in adolescents with ASD relative to controls overall (see Table 4, Figure 3).

4.3.2.1 Angry faces

In the earliest time window (80-120 ms), adolescents with ASD showed significant left middle temporal, bilateral middle, right inferior, and left superior frontal activation while controls showed only left inferior frontal activation (see Table 3a). The left middle frontal and left superior frontal activation seen within groups in ASD were also significantly greater than that seen in controls (see Table 4a, Figure 3a).

In 120-160 and 160-200 ms, within group analyses showed only significant activations in controls, with bilateral medial frontal activation in both time windows and left middle, right inferior and right superior frontal activation during 160-200 ms (see Table 3a). There were no significant between group contrasts for both time windows.

During 200-240 ms, both groups showed significant orbitofrontal activation, with the ASD group showing left superior frontal (BA10) activation while controls showed significant right middle frontal (BA10) activation (see Table 3a). Both of these activations were also significant in between-group contrasts (see Table 4a, Figure 3a).

Bilateral middle, left medial, and left superior frontal activation was observed in the ASD group while controls showed left medial and middle, and right inferior frontal activity during 240-280 ms (see Table 3a). Between group contrasts revealed significantly greater right inferior, left medial and left superior frontal activation in the ASD group relative to controls (see Table 4a, Figure 3a).

4.3.2.2 Happy faces

From 80-120 ms, bilateral middle, left medial, and right inferior frontal activations were seen in adolescents with ASD, while bilateral inferior frontal, right superior temporal, and right superior frontal activations were observed in controls (see Table 3b). Between-group contrasts showed significantly greater right superior and inferior frontal activations in the ASD group, compared to controls (see Table 4b, Figure 3b).
Only right medial frontal activity was seen in the ASD group from 120-160 ms, with no significant between-group contrasts. Lack of between-group findings continued into 160-200 ms, although within group analyses showed significant left superior and left medial frontal activation in adolescents with ASD and controls, respectively (see Table 4b, Figure 3b).

Between 200-240 ms, orbitofrontal and bilateral middle, left medial, and right inferior frontal activations were observed in the ASD group while controls showed significant bilateral middle and left medial frontal activations (see Table 3b). Adolescents with ASD showed significantly greater left superior frontal activation, compared to controls (see Table 4b, Figure 3b).

From 240-280 ms, left medial and right middle frontal activations were observed in the ASD group while left middle and medial frontal activations were noted in the control group (see Table 3b). There were no significant between-group findings.
**Table 3.** Locations of significant \((p < .05,\) uncorrected\) peak activations for adolescents with ASD and controls in response to (a) angry and (b) happy faces.

<table>
<thead>
<tr>
<th>Time window (ms)</th>
<th>Group</th>
<th>Laterality</th>
<th>Area</th>
<th>TAL (x y z)</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASD</td>
<td>L</td>
<td>MidTG</td>
<td>-45 -20 -15</td>
<td>20 *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MidFG</td>
<td>40 30 30</td>
<td>9</td>
</tr>
<tr>
<td>80-120</td>
<td>ASD</td>
<td>R</td>
<td>MidFG</td>
<td>25 55 -5</td>
<td>10 *</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>R</td>
<td>ITG</td>
<td>45 -10 -20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidFG</td>
<td>-45 25 15</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-20 40 35</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>L</td>
<td>IFG</td>
<td>-45 20 5</td>
<td>45</td>
</tr>
<tr>
<td>120-160</td>
<td>Controls</td>
<td>R</td>
<td>MedFG</td>
<td>5 -15 55</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>Fusiform gyrus</td>
<td>40 -5 -20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>Insula</td>
<td>-40 -15 5</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MedFG</td>
<td>0 55 -10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>L</td>
<td>MidFG</td>
<td>-35 0 40</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MedFG</td>
<td>10 -20 55</td>
<td>6</td>
</tr>
<tr>
<td>160-200</td>
<td>Controls</td>
<td>R</td>
<td>IFG</td>
<td>45 30 5</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>SFG</td>
<td>25 50 -15</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MedFG</td>
<td>-15 55 5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>ASD</td>
<td>L</td>
<td>SFG</td>
<td>-25 55 5</td>
<td>10 *</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>R</td>
<td>MidFG</td>
<td>35 50 0</td>
<td>10 *</td>
</tr>
<tr>
<td>200-240</td>
<td>ASD</td>
<td>L</td>
<td>MedFG</td>
<td>0 -15 55</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MidFG</td>
<td>45 35 -5</td>
<td>47 *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidFG</td>
<td>-40 30 20</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-25 50 15</td>
<td>10 *</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>L</td>
<td>MedFG</td>
<td>0 -10 60</td>
<td>6  *</td>
</tr>
<tr>
<td>240-280</td>
<td>ASD</td>
<td>L</td>
<td>MedFG</td>
<td>50 15 15</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-45 20 20</td>
<td>46 *</td>
</tr>
</tbody>
</table>

*Note.* L = left, R = right, F = frontal, G = gyrus, I = inferior, Med = medial, Mid = middle, S = superior, * significant within-group activation matched to significant between-group contrasts, depicted in figures, ⬠ denotes similar regional activation between groups.
b) Happy faces

<table>
<thead>
<tr>
<th>Time window (ms)</th>
<th>Group</th>
<th>Laterality</th>
<th>Area</th>
<th>TAL</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>120-160</td>
<td>ASD</td>
<td>R</td>
<td>Insula</td>
<td>40 -5</td>
<td>-5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MedFG</td>
<td>5 40 30</td>
<td>9</td>
</tr>
<tr>
<td>160-200</td>
<td>ASD</td>
<td>R</td>
<td>IFG</td>
<td>50 5 30</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MedFG</td>
<td>0 -25 60</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidFG</td>
<td>-30 20 45</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>Orbital gyrus</td>
<td>5 35 -35</td>
<td>11 *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MidFG</td>
<td>30 60 10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidFG</td>
<td>-35 35 -10</td>
<td>11</td>
</tr>
<tr>
<td>200-240</td>
<td>ASD</td>
<td>R</td>
<td>MidFG</td>
<td>35 5 55</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidFG</td>
<td>-40 10 40</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MedFG</td>
<td>-10 5 5</td>
<td>10</td>
</tr>
<tr>
<td>240-280</td>
<td>ASD</td>
<td>L</td>
<td>MedFG</td>
<td>0 -10 55</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MidFG</td>
<td>40 30 10</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidFG</td>
<td>-40 0 45</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MedFG</td>
<td>-10 5 5</td>
<td>10</td>
</tr>
</tbody>
</table>

Note. L = left, R= right, F = frontal, G= gyrus, I = inferior, Med = medial, Mid = middle, S = superior, * significant within-group activation matched to significant between-group contrasts, depicted in figures, O denotes similar regional activation between groups.
Table 4. Locations of significant \((p < .05\), uncorrected) peak activations for ASD versus controls in response to angry faces (a) and ASD versus controls in response to happy faces (b).

<table>
<thead>
<tr>
<th>Time window (ms)</th>
<th>Contrast</th>
<th>Laterality</th>
<th>Area</th>
<th>TAL</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-120</td>
<td>ASD&gt;CON</td>
<td>R</td>
<td>MedFG</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidTG</td>
<td>-25</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>SFG</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>IFG</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>CON&gt;ASD</td>
<td>R</td>
<td>MidTG</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>SFG</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>120-160</td>
<td>ASD&gt;CON</td>
<td>R</td>
<td>MidFG</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MidFG</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>IFG</td>
<td>-55</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MedFG</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidTG</td>
<td>-40</td>
<td>30</td>
</tr>
<tr>
<td>160-200</td>
<td>ASD&gt;CON</td>
<td>L</td>
<td>MidFG</td>
<td>-35</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>IFG</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidTG</td>
<td>-45</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MedFG</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MedFG</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-25</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-25</td>
<td>65</td>
</tr>
<tr>
<td>200-240</td>
<td>ASD&gt;CON</td>
<td>R</td>
<td>MidFG</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>IFG</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MedFG</td>
<td>-5</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>Cingulate gyrus</td>
<td>-10</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-25</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>CON&gt;ASD</td>
<td>R</td>
<td>MidFG</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>SFG</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>240-280</td>
<td>ASD&gt;CON</td>
<td>R</td>
<td>IFG</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MedFG</td>
<td>-5</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>Cingulate gyrus</td>
<td>-10</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-25</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>CON&gt;ASD</td>
<td>L</td>
<td>MidTG</td>
<td>-65</td>
<td>40</td>
</tr>
</tbody>
</table>

Note. L = Left, R= Right, F = frontal, G= gyrus, I = inferior, Med = medial, Mid = middle, S = superior, * significant within-group activation matched to significant between-group contrasts, depicted in figures.
b) ASD versus controls in response to happy faces

<table>
<thead>
<tr>
<th>Time window (ms)</th>
<th>Contrast</th>
<th>Laterality</th>
<th>Area</th>
<th>TAL (x y z)</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-120</td>
<td>ASD&gt;CON</td>
<td>L</td>
<td>STG</td>
<td>-50 -5 -10</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>Cingulate Gyrus</td>
<td>15 -5 50</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-20 45 30</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>SFG</td>
<td>35 45 -20</td>
<td>11 *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>IFG</td>
<td>60 15 20</td>
<td>45 *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>STG</td>
<td>70 -25 5</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>CON&gt;ASD</td>
<td>R</td>
<td>STG</td>
<td>65 15 -15</td>
<td>38 *</td>
</tr>
<tr>
<td>120-160</td>
<td>ASD&gt;CON</td>
<td>L</td>
<td>Fusiform gyrus</td>
<td>-40 -60 -10</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>IFG</td>
<td>-50 35 -5</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidTG</td>
<td>-40-70 30</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MedFG</td>
<td>0 -10 55</td>
<td>6</td>
</tr>
<tr>
<td>160-200</td>
<td>ASD&gt;CON</td>
<td>L</td>
<td>STG</td>
<td>-55 -5 -5</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>STG</td>
<td>60 10 -10</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>MidFG</td>
<td>-40 45 25</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>CON&gt;ASD</td>
<td>R</td>
<td>MidFG</td>
<td>45 45 15</td>
<td>46</td>
</tr>
<tr>
<td>200-240</td>
<td>ASD&gt;CON</td>
<td>L</td>
<td>MidTG</td>
<td>-45 -70 25</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-25 40 40</td>
<td>8  *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>MidTG</td>
<td>-60 -40 0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>SFG</td>
<td>20 40 40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>STG</td>
<td>70 -50 15</td>
<td>22</td>
</tr>
<tr>
<td>240-280</td>
<td>ASD&gt;CON</td>
<td>R</td>
<td>MedFG</td>
<td>5 -10 50</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>IFG</td>
<td>-50 5 30</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>STG</td>
<td>-65 -35 10</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>STG</td>
<td>-65 -10 0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>ITG</td>
<td>-45 -15 -35</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>SFG</td>
<td>-40 55 15</td>
<td>10</td>
</tr>
</tbody>
</table>

Note. L = Left, R= Right, F = frontal, G= gyrus, I = inferior, Med = medial, Mid = middle, S = superior, * significant within-group activation matched to significant between-group contrasts, depicted in figures.
a) Angry faces

<table>
<thead>
<tr>
<th>Group</th>
<th>Time windows (ms)</th>
<th>ASD</th>
<th>Controls</th>
<th>Contrasts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>80-120</td>
<td>none</td>
<td>LIFG</td>
<td>RIFG, LMedFG</td>
</tr>
<tr>
<td></td>
<td>160-200</td>
<td></td>
<td>LMidFG, RMedFG</td>
<td>RMedFG</td>
</tr>
<tr>
<td></td>
<td>200-240</td>
<td></td>
<td>LMidFG, RSFG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>240-280</td>
<td></td>
<td>RMedFG</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Significant areas of activation in within-group analyses (rows 1 and 2) in comparison to significant between-group analyses (row 3) to a) angry and b) happy faces.
b) Happy faces

<table>
<thead>
<tr>
<th>Group</th>
<th>80-120</th>
<th>120-160</th>
<th>160-200</th>
<th>200-240</th>
<th>240-280</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbital gyrus, RIFG</td>
<td>RMedFG</td>
<td>LSFG</td>
<td>LMidFG, RIFG</td>
<td>RMedFG</td>
<td></td>
</tr>
<tr>
<td>RMedFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMedFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMedFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMedFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMedFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMidFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMidFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMidFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMidFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMidFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Significant areas of activation in within-group analyses (rows 1 and 2) in comparison to significant between-group analyses (row 3) to a) angry and b) happy faces.
Chapter 5
Discussion

Emotional faces convey a wide array of social information and are important cues for social interactions, in which individuals with ASD experience deficits. Our study examined the differences in neural activity during happy and angry face processing between adolescents with ASD and typically developing adolescents. We found significant between group differences starting as early as 80 and continuing until 280 ms. Our focus was on the frontal areas due to the notion of the prefrontal cortex being involved in higher cognitive processes such as emotional evaluation as well as suggestions that atypical emotional face processing may be due to differences in processes recruiting the frontal lobes (Ochsner & Gross, 2005).

5.1 Parental response forms

Analysis of the parental response forms showed significant impairments in adolescents with ASD in multiple domains of specific aspects of executive functioning, such as inhibition, shifting, emotional control and working memory, as well as broader indices such as behaviour regulation and meta-cognition, and global executive functioning. Such deficits in executive functioning are consistent with previous studies (e.g., Hughes et al., 1994). Further significant differences in parental reports of hyperactive symptomology as well as repetitive behaviour emphasize the extent of behavioural impairment in adolescents with ASD. Most notably, parents also reported significant impairment in all aspects of social responsiveness, highlighting the extent of social behavioural problems in adolescents with ASD. Collectively, findings in parental response forms are in accordance with the diagnostic criteria of ASD.

5.2 Behavioural findings

A lack of significant differences in response latencies between groups for either emotion is consistent with previous studies that have reported no effect of emotion on response time (Guyer, Monk, McClure-Tone, et al., 2008; Luo, Holroyd, Jones, Hendler, & Blair, 2007; Wong et al., 2008 but see Monk et al., 2003). This non-significant finding may be attributable to the task not being subtle enough to parse out group effects; minimal cognitive demands required to
perform the task may also have contributed to the null behavioural findings. Nevertheless, the neuroimaging data demonstrated discrepancies in neural mechanisms between the groups.

5.3 Source localization in typically developing adolescents

Source localization for neural activations in response to angry and happy faces in our typically developing adolescents was found to be consistent with the findings reported in the current literature. To angry faces, we found bilateral medial, middle, inferior and right superior frontal activations in typically developing individuals, areas of activation that have been implicated in anger processing (Fusar-Poli et al., 2009; Kesler/West et al., 2001; Kilts, Egan, Gideon, Ely & Hoffman, 2003; Sprengelmeyer et al., 1998). We also found bilateral inferior and middle frontal, left medial, right superior frontal and right superior temporal activations in response to happy faces in typically developing adolescents, which have also been reported earlier (Kilts, Egan, Gideon, Ely & Hoffman, 2003; Surguladze et al., 2003).

While the amygdalae have been implicated in emotional processing of anger (Gur et al., 2002; Hariri et al., 2000), the lack of significant amygdala activation in the present study may be due to the attentional demands in the task as limbic activation is affected by both task and attentional demand. Given the simplicity of the task, the finding of no amygdala involvement in angry processing is consistent with other findings (Blair et al., 1999; Vuilleumier, Armony, Driver, & Dolan, 2001; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004).

5.4 Early emotional differentiation during emotional processing in control adolescents

Current literature has documented early differentiation between emotional expressions in neural responses. EEG studies have shown a negative occipito-temporal peak from 200-240 ms in response to emotional, relative to neutral faces (Marinkovic & Halgren, 1998) in addition to emotion-specific early ERP components (Ashley, Vuilleumier, & Swick, 2004; Eimer & Holmes, 2002; Batty & Taylor, 2003). These prior findings were supported in our data, which showed that happy faces recruited the right middle frontal gyrus and angry faces implicated the
right inferior frontal gyrus during 200-240 ms. Further, our results showing left medial frontal (BA 10) activation in the 160-200 ms time window was consistent with a previous study finding activity within the same region from 138-205 ms (Esslen, Pascual-Marqui, Hell Kochi, & Lehmann, 2004).

The large occipito-temporal negative wave from 200-400 ms has also been observed in an MEG study by Halgren et al. (2000), which peaked at 240 ms in response to emotional relative to neutral faces. Earlier stronger cortical activity in response to emotional, relative to neutral and blurred faces between 100 to 360 ms was similarly observed by Streit et al. (2003). Early emotion-specific processing (120-170 ms) has also been shown in event-related magnetic fields (Peyk, Schupp, Elbert, & Junghöfer, 2008), consistent with our findings of bilateral medial frontal activation in response to angry faces, but no significant activations to happy faces.

Our finding of early (80-120 ms) superior temporal activation in response to happy faces, is consistent with findings of superior temporal and medial prefrontal involvement differentiating between emotions within 100 ms (Liu & Ioannides, 2010). This finding is also consistent with reports of P1, an early parieto-occipital ERP component, at around 110 ms is associated with implicit emotional processing in children (Batty & Taylor, 2006) and adults (Batty & Taylor, 2003). Bayle and Taylor (2010) also found early frontal activation sensitive to implicit, but not explicit, processing of emotional faces.

### 5.5 Atypical spatiotemporal profile of emotional face processing in ASD

Aberrant neural mechanisms underlying implicit emotional face processing have been found in a number of studies with participants with ASD. An early negative component to fearful, relative to neutral, faces that has been observed in typically developing children was not noted in children with ASD (Dawson, Webb, Carver, Panagiotides, & McPartland, 2004), and a delayed and reduced P1 was found in children with ASD during an implicit emotional face processing task (Batty, Meaux, Wittemeyer, Rogé, & Taylor, 2011, but see O’Connor, Hamm, & Kirk, 2005). Delayed and smaller N170 components have been similarly found in adults with
ASD in response to all emotional faces (O’Connor Hamm, & Kirk, 2005). The current literature thus indicates atypical early processing of emotional faces in ASD.

We found fewer significant differences between neural activation to happy, relative to angry, faces between the two groups, suggesting that adolescents with ASD process happy faces more similarly to typically developing adolescents, which is consistent with literature documenting typical processing of happy faces in individuals with ASD (Critchley et al., 2000; Farran, Branson, & King, 2011). Fewer between-group differences in response to happy faces may be attributed to negative emotions requiring a more complex processing, which is supported by findings that the ability to accurately identify happy expressions matures earlier in comparison to identification of negative emotions such as angry and fear, which mature at later ages (Markham & Adams, 1992).

We did not find any significant between group differences in the frontal activity between 120-160 ms and 160-200 ms, suggesting recruitment of comparable neural structures during those time windows. Greater variability of peaks in the ASD group at 174±67 ms to emotional faces may have contributed to our lack of significant contrasts within these time windows (Wong, Fung, Chua, & McAlonan, 2008). Peak activations to angry or happy faces in controls, while significant within-group, may not have been strong enough to drive significant between-group contrasts. Our task may have contributed to a lack of contrasts during these time windows for two reasons: 1) it involved implicit emotional face processing; and 2) stimuli presentation occurred at a rapid rate of 80 ms, which may have elicited neural activity too subtle to detect any significant group differences.

5.5.1 Between group comparisons towards happy faces

Relative to angry faces, we found fewer significant differences between frontal activation in the two groups to happy faces. Early significant between-group differences occurred between 80-120 ms, during which adolescents with ASD exhibited greater right superior and inferior frontal activation relative to controls. Greater frontal activation in adolescents with ASD may reflect initial frontal negative peaks in typical individuals at 100 ms (Bayle & Taylor, 2010; Münte et al., 1998). In contrast, controls showed greater superior temporal activation, relative to
the ASD group, which is consistent with an earlier finding of reduced superior temporal activation in individuals with ASD to faces (Pierce, Müller, Ambrose, Allen, & Courchesne, 2001). Greater superior temporal activation in controls during social processing is further supported by study by Castelli et al. (2002), who found reduced superior temporal activation in ASD relative to controls in a task that involved attributing mental states to geometric objects.

5.5.2 Between group comparisons towards angry faces

Our finding of greater left middle temporal activation to angry faces in adolescents with ASD, relative to controls, is consistent with the results of an emotional face matching task (Wang et al., 2004) but contradict an earlier finding of greater left middle temporal activation in controls during explicit emotional face processing (Critchley et al., 2000). These studies suggest the involvement of different neural structures during explicit and implicit emotional face processing, also confirmed by our group (Bayle & Taylor, 2010).

A finding of interest was that the significant between-group contrasts between 200-240 ms occurred in regions that were homologous. That is, in adolescents with ASD, greater activation occurred in the left BA 10 (superior frontal gyrus) while in typically developing controls, greater activation occurred in the right BA 10 (middle frontal gyrus). As the left and right hemispheres have been implicated in feature and holistic processing of faces, respectively, our findings support the notion that typically developing individuals utilize holistic strategies during face processing to a greater extent than visuospatial processing, the opposite of which is found in ASD (Hubl et al., 2003; Jeeves, 1984). Differential strategy use was further supported by findings between 240-280 ms, during which adolescents with ASD showed greater medial frontal activation, consistent with the results of a visual search task (Hubl et al., 2003). These later findings are consistent with the notion that individuals with ASD utilize alternative face processing strategies, endorsing local (feature-based) rather than global (holistic) information processing (Hubl et al., 2003).
5.5.3  Spatiotemporal profile of orbitofrontal activation in response to angry faces

The prefrontal cortex is thought to play a role in higher cognitive processes such as emotional evaluation (Ochsner & Gross, 2005). The orbitofrontal cortex, in particular, has been implicated in mediating emotional behaviour, behaviours of social inhibition and reversal learning (Dias et al., 1996; Elliot, Dolan, & Frith, 2000). Because anger is expressed to elicit an altering of inappropriate behaviour, the orbitofrontal cortex is thought to play a role in anger processing (Blair, Morris, Frith, Perrett, & Dolan, 1999). Right orbitofrontal cortex (BA47) activity has been found in the processing of angry, but not sad or neutral faces (Blair, Morris, Frith, Perrett, & Dolan, 1999). Our findings of orbitofrontal activation in controls to angry faces are consistent with evidence of activation towards angry faces in the same region (although left lateralized) at 170-180 ms, peaking around 200-210 ms and offset at 230-240 ms (Luo, Holroyd, Jones, Hendler, & Blair, 2007).

In controls, left orbitofrontal activation was first observed in left BA10 from 120-160 ms, bilateral activation during 160-200 ms, continued into 200-240 ms (right only). In contrast, adolescents with ASD show a similar but delayed trend, with left BA10 activation starting at 200-240 ms, then bilateral activation from 240-280. This temporally shifted and contralateral orbitofrontal activation between the two groups indicates delayed orbitofrontal activation towards angry faces in adolescents with ASD relative to controls.

5.6  Summary of findings

Comparable performance between the ASD group and the typically developing group on the Affect Recognition subtest of the NEPSY-II (Korkman, Kirk, & Kemp, 2007) and response latencies on the Emotional Face Task suggested that between-group differences in neural activity on the Emotional Face Task were not attributable to task difficulty. Our data suggest that processing of happy faces is less complex and more similar between adolescents with and without ASD, relative to angry faces. Towards angry faces, we found temporally delayed and contralateral activation of the orbitofrontal cortex, an area that has been implicated in anger
processing. Furthermore, our data suggest different emotional face processing strategies in individuals with ASD, who may use more local, feature-based processing strategies in comparison to typically developing individuals, endorse more holistic strategies when processing emotional faces.

5.7 Limitations and Future Directions

The results of this study should be interpreted with the understanding that the clinical sample was comprised of high-functioning adolescents with autism, who were able to tolerate neuroimaging scanning environments. Given the wide range of clinical presentation in ASD, the results of the present study can only be extended to the high-functioning end of the autism spectrum.

It should further be noted that three of the 13 participants in the ASD group were not medication naïve at the time of the study. Given the high prevalence rate of comorbid diagnoses with ASD in as well as common use of medication in ASD intervention, it would of interest to additionally recruit children and adolescents with comorbid disorders (i.e. ADHD) or who are on medication (i.e. stimulants) (Logan et al., 2012; Moseley, Tonge, Brereton, & Einfeld, 2011). The value of studying the former lies in being able to explore the interactions between the disorders and how this interaction manifests in clinical presentation. Recruiting children who are on medication as an intervention for ASD symptomology will allow us to examine the effect of certain types of medication on neural activity associated with emotional face processing.

Despite being comparable to male counterparts in the core triad symptoms of ASD, females with high functioning ASD have particularly pronounced social problems (Holtmann, Bölte, & Poustka, 2007; McLennan, Lord, & Schopler, 1993). This suggests possible sex differences in the social domain, despite similar deficits in social interactions to males with high functioning ASD. Hence an interesting future study would be to examine matched group of male and female participants with ASD.

While only happy and angry faces were chosen as positive and negative affective stimuli, it would be of interest to determine the neural underpinnings of valence effects of the stimuli as well as other facial affect processing. Studying other negatively and positively-valenced affective
stimuli would be of interest, particularly given previous findings of negative affect processing deficits (Sigman, Kasari, Kwon, & Yirmiya, 1992).

The current sample included only participants who were in early adolescence. Shifting involvement of neural structures across typical development, albeit using fearful, rather than angry faces, supports future investigation into the neural mechanisms underlying the breadth of the developmental trajectory of emotional face processing in ASD through the recruitment of children and adults (Monk, et al., 2003).

There are currently inconsistencies in the literature as to the use of neutral faces as baseline (e.g., Hung et al., 2010; Luo, Holroyd, Jones, Hendler, & Blair, 2007). Our findings indicate that rather than considering neutral faces as a non-affective control, they should be considered as a separate and unique emotion. Hence, a future direction would be to run further analyses to investigate the differences in neural activation elicited by neutral faces, in comparison to happy and angry faces.

A final future research direction would be to study the effects of visual field of affective stimuli presentation on emotional face processing. Previous neuroimaging and lesion studies have suggested a unique hemispheric advantage in processing positive and negative affective stimuli, with the left for the former and right for the latter (Noesselt, Driver, Heinze, & Dolan, 2005; Reuter-Lorenz, Givis, & Moscovitch, 1983). Expanding on such findings would further current understanding of laterality advantages in emotional face processing, particularly in individuals with ASD.

5.8 Conclusions

The present study examined the time course of neural activation during emotional face processing in adolescents with ASD and typically developing adolescents. Despite similar behavioural performance, significant differences in neural activation were found in both spatial and temporal domains. These results suggested an atypical but rapid emotional face processing mechanism in adolescents with ASD. Of particular interest was our finding of more similar neural activity during happy, relative to angry, face processing suggesting more typical processing of happy faces in individuals with ASD, relative to controls. The present study is the first study to use MEG to determine the spatiotemporal differences of the neural processing of
emotional face processing in adolescents with ASD compared to controls using magnetoencephalography. These findings will contribute significantly to the field of emotion research in typical and atypical development as well as the neural mechanisms underlying this fundamental human ability.
References


emotional go-nogo task. *Biological Psychiatry, 63*, 927–934.


Developmental Disorder, 37, 855–866.
Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L.,
Lancaster, J.L., Rainey, L.H., Summerlin, J.S., Freitas, C.S., Fox, P.T., Evans, A.C., Toga, A.W.,
the development and evaluation of a forward-transform method. Human Brain Mapping,
5, 238–242.
Liu, L., & Ioannides, A. A. (2010). Emotion Separation Is Completed Early and It Depends on
Logan, S. L., Nicholas, J. S., Carpenter, L. a, King, L. B., Garrett-Mayer, E., & Charles, J. M.
(2012). High prescription drug use and associated costs among Medicaid-eligible
children with autism spectrum disorders identified by a population-based surveillance
Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., Pickles, A., &
measure of social and communication deficits associated with the spectrum of autism.
version of a diagnostic interview for caregivers of individuals with possible pervasive
processing as revealed by gamma band synchronization using MEG. Neuroimage, 34,
839–847.
Markham, R., & Adams, K. (1992). The effect of type of task on children's identification of
Mazefsky, C. A., & Oswald, D. P. (2008). Emotion perception in Asperger’s syndrome and high-


advances in biomagnetism. 11th International Conference on Biomagnetism. Sendai: Tohoku Univ. Press.


