Emotion attribution from facial expressions in individuals with social communication impairment

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Abstract

Social communication impairment (SCI) is recognised as the core deficit in all autism spectrum disorders (ASD) (1, 2). Recent research also supports the conceptualisation of autism as the upper extreme of a social communication continuum and advocates the study of SCI as a dimension of behaviour (3). The underlying neurobiology of SCI has proved elusive in ASD and has not yet been investigated for SCI measured as a dimension of behaviour. Ultimately, integrated behavioural, cognitive, and functional approaches, in which all levels of explanation constrain and inform each other (4, 5), are required to elucidate the underlying aetiology of SCI.

Previous functional magnetic resonance imaging (fMRI) research has focused on reduced right fusiform gyrus (FG) specialisation for face processing as a possible explanation for the SCI in ASD (6-8). However, recent fMRI research using static face percepts has reported comparable right FG activation to typically developing individuals when individuals with ASD attended to the eyes region of the face (9) and view the faces of familiar people (10). Consequently, face processing deficits and the associated right FG hypo-activation hypothesis has become a contentious explanation for the SCI seen in autism. Another plausible explanation for SCI in ASD is reduced expertise in the attribution of emotion from facial expressions. Whilst this has been acknowledged as a potential explanation for the SCI seen in autism (1), there has actually been little integrated research investigating the relationship between SCI and the neural substrates of expertise in attribution of emotion from facial expressions in individuals with ASD (11).

Social communication involves the perceptual, emotion and cognitive processing of the facial expressions of other people to attribute the correct emotion (2). Emotion attribution from static facial expressions has been shown to activate the FG, amygdala and prefrontal cortex in typically developing individuals associated with perceptual, emotion and cognitive processing of facial expressions respectively (12). Activation in these three regions of interest (ROI) is, potentially, informative when investigating the underlying aetiology of SCI. Therefore, they were chosen *a priori* as ROI during the attribution of emotion attribution from facial expressions with the categorical and dimensional studies respectively.

In the categorical studies, 16 high functioning individuals with an ASD diagnosis and 10 typically developing controls attributed emotion from static facial expressions while neural activation in these three hypothesis-driven ROI was measured. Individuals with ASD demonstrated comparable expertise and had comparable ROI activation during the emotion attribution task that required configural processing [the emotion label task]. However, these same individuals demonstrated reduced expertise and reduced right FG activation during the emotion attribution task that did not require configural processing [the emotion match task], and reduced right FG activation in a task that required them to attend to the eyes region of the face to attribute gaze direction. The findings provided evidence that individuals with ASD configurally process face percepts when necessary for the completion of the task, but use atypical face processing strategies in tasks that have greater perceptual load and do not necessitate configural processing. These findings support that task-dependant perceptual processing

abnormalities in ASD are not related to reduced attention to the eyes region of the face *per se*; however, did not rule out that these abnormalities may relate to reduced configural processing/ attention to the whole face stimuli in individuals with ASD.

The dimensional studies were undertaken to further investigate the relationship between FG responsivity and expertise in the attribution of emotion from facial expressions. SCI was quantified in 60 individuals with social communication difficulties (SCD)(probands) using the Social Responsivity Scale (SRS) (13). Probands that did, and those that did not, fulfil ADI-R diagnostic criteria for autism were found to have SCI, using the SRS, in the severity range previously reported for ASD (14). Activation in right FG ROI was further investigated in 10 probands and their brothers while they attributed emotion from inverted and non-inverted dynamic facial expression. These dynamic facial expressions, which were presented in a paradigm called the Dynamic Facial Expression Paradigm (DFEP), required configural processing and continuous attention to the whole face. Individuals with SCI had a similar capacity to accurately attribute emotion from non-inverted dynamic facial expressions as their brothers. Although there was no statistically significant difference in expertise between the proband and brother group, the trend toward increased response time in the non-inverted condition of the DFEP in the SCI group suggests the use of an accuracy/ response time trade-off strategy. SCI was directly correlated with right FG activation across the groups and the proband group activated significantly greater right FG activation to achieve a comparable level of performance as the brother group in the non-inverted condition of the DFEP. This finding may be related to increased configural processing and/ or the greater attentional demands inherent in attributing emotion from non-inverted dynamic facial expressions. The inverse was found in the inverted condition of the DFEP providing evidence for different perceptual processing strategies between groups when also processing inverted dynamic facial expressions.

Both the categorical and dimensional studies provide evidence in support of the functional specialisation of the right FG for the configural processing of facial expressions, and atypical task-dependent perceptual processing in these high functioning individuals with SCI. Differing configural processing and attentional demands inherent in the experimental paradigms and atypical perceptual strategies offer possible explanations for atypical perceptual processing and differing right FG activation seen in these and other studies of face and facial expression processing (6-8).

In the future, larger studies are required to further investigate accuracy/ speed trade-offs and determine if high functioning individuals with SCI are less expert in the attribution of emotion from facial expressions. Connectivity and fMRI studies utilising experimental designs such as parametric load analysis and incorporating eye-tracking technology are also required to further elucidate the relationship between behaviour, cognition, and neural function in individuals with SCI. Specifically, further integrated research is needed to determine the relationship between right FG activation, configural processing of facial expressions and attention to faces in individuals with SCI.

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Abbreviations

AC-PC	anterior commissure-posterior commissure
ADHD	attention deficit hyperactivity disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS-G	Autism Diagnostic Observation Schedule-Generic
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APA	American Psychiatric Association
AS	Asperger's syndrome
ASD	autism spectrum disorder(s)
BA	Brodmann's areas
BAP	broader autistic phenotype
BOLD	blood oxygenation level dependant
CC	central coherence
CCI	cognitive construct of interest
DFEP	Dynamic Facial Expression Paradigm
DSM	Diagnostic Statistical Manual
DTI	Diffusion Tensor Imaging
DZ	dizygotic
EAP	Emotion Attribution Paradigm
EEG	electro-encephalogram
EF	executive function
EHI	Edinburgh Handed Inventory
EL	emotion label

EM	emotion match
FA	flip angle
FDR	first-degree relatives
FFA	fusiform 'face' area
FG	fusiform gyrus
fMRI	functional magnetic resonance imaging
FOV	field of view
FSIQ	full scale intelligence quotient
GAP	Gaze Attribution Paradigm
GLM	General Linear Model
HFA	high functioning autism
HRF	haemodynamic response function
ICD	International Classification of Disease
IQ	intelligence quotient
ISI	inter-stimulus interval
ITG	inferior temporal gyrus
LH	left handed
MEG	magneto-encephalography
MRI	magnetic resonance imaging
MZ	monozygotic
NAAR	National Alliance of Autism Research
NLD	non-verbal learning disorder
NMR	nuclear magnetic resonance
OMIM	online mammalian inheritance in man

PDD-NOS	pervasive developmental disorder-not otherwise specified
PIQ	performance intelligence quotient
RH	right handed
ROI	regions of interest
SAT	Social Attribution Task
SCD	social communication difficulties
SCI	social communication impairment
SCQ	Social Communication Questionnaire
SD	standard deviations
SE	standard errors
SNR	signal noise ratio
SPGR	spoiled gradient recalled
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for Social Sciences
SRS	Social Responsivity Scale
TE	time to echo
TOM	theory of mind
TR	time to response
WBA	whole brain analysis
WHO	World Health Organisation
WAIS	Wechsler Abbreviated Intelligence Scale
WISC–III	Wechsler Intelligence Scale for Children-Third Edition
WASI–III	Wechsler Adult Intelligence Scale-Third Edition
VIQ	verbal intelligence quotient

Statement of Work

I would like to acknowledge my own and others contribution to this research. The categorical studies were undertaken in collaboration with Dr. Hower Kwon and Dr. Linda Lotspeich at Stanford University Department of Psychiatry and Behavioural Sciences. I was involved in the characterisation, scanning and analysis of all brain scans from the sample in the categorical studies and undertook statistical analysis (under the supervision of M/s. Christine Blasey, Statistician in the Stanford University Department of Psychiatry and Behavioural Sciences) and interpretation of all data in the categorical studies. In the first categorical study, the Emotion Attribution Paradigm (EAP) was used. This paradigm was developed by Dr. Ahmad Hariri and colleagues at University of California Los Angeles (UCLA) and supplied by Professor Susan Bookheimer (UCLA). In the second categorical study, the Gaze Attribution Paradigm (GAP) was used. This paradigm was developed by numerous research assistants in the Stanford University Neuroimaging Laboratory for a study of typically developing individuals.

In the dimensional studies, I undertook the recruitment, behavioural assessments and characterisations, cognitive testing, developed the Dynamic Facial Expressions Paradigm (DFEP) and undertook the scanning, processing of all brain scans, statistical analysis between groups, and interpretation of all data (under the supervision of Dr. Vinod Menon, Associate Professor, Stanford University Department of Psychiatry and Behavioural Sciences) with the assistance of research assistants and volunteers. I would like to thank research assistants - Mr. Dean Mobbs and M/s. Asya Karchemskiy and research volunteers - Mr. Brian Evans, M/s. Kristyn Dixon, M/s. Christine Serventi, and M/s. Maya Donahue in particular for their outstanding help in the following studies.

Acknowledgments

During a visit to Stanford University to develop acumen in neuroimaging, funded by the Maria Henderson Travelling Fellowship in October 2000, I met many parents of high functioning young men with ASD. Parents reported that this group of young men were under-researched and that they were keen to remedy this situation. Firstly, I would like to thank these families for their encouragement to undertake this research and for their willingness to participate.

I would also like to thank Professors Joachim Hallmayer and Allan Reiss in the Stanford University Department of Psychiatry and Behavioural Sciences, and Professor Michael Connor in the Glasgow University Department of Medical Genetics, who provided supervision and academic mentorship throughout the period of this research from October 2001-October 2006. I am also grateful to Professor Allan Reiss for his sponsorship, which enabled me to undertake the fMRI research presented in this thesis in the Neuroimaging Laboratory at Stanford University.

I would also like to thank those professionals that facilitated the recruitment of young men with ASD and their families. In particular, I would like to thank Mrs. Paula Jacobsen, Adjunctive Professor in the Stanford University Department of Psychiatry and Behavioural Sciences, for her enthusiasm about this research and for mentioning it to the families of individuals with ASD whom attended her practice. I would also like to thank her for her friendship and her encouragement, mentorship, and support throughout this research.

Amongst the non-professionals , too numerous to list, who provided indispensable support, I am particularly grateful to Mrs. Hilda Gould and Mrs. Sonia Crottez-Herbette and thank them for their exceptional friendship. Last, but not least, I would like to thank my husband Mr. Robert Carr for his help, patience and encouragement throughout this research, and my baby daughter Ruby for exemplifying the importance of social communication in infant development.

Publication

Emotional Attribution in High-Functioning Individuals with Autistic Spectrum Disorder: A Functional Imaging Study

Judith Piggot, M.B. CH.B., Hower Kwon, M.D., Dean Mobbs, B.SC., Christine Blasey, PH.D., Linda Lotspeich, M.D., Vinod Menon, PH.D., Susan Bookheimer, PH.D., Allan L. Reiss, M.D.

Objective: To determine whether expertise in the attribution of emotion from basic facial expressions in high-functioning individuals with autistic spectrum disorder (ASD) is supported by the amygdala, fusiform, and prefrontal regions of interest (ROI) and is comparable to that of typically developing individuals.

Method: Functional magnetic resonance imaging scans were acquired from 14 males with ASD and 10 matched adolescent controls while performing emotion match (EM) (perceptual), emotion label (EL) (linguistic), and control tasks. Accuracy, response time, and average activation were measured for each ROI.

Results: There was no significant difference in accuracy, response time, or ROI activation between groups performing the EL task. The ASD group was as accurate as the control group performing the EM task but had a significantly longer response time and lower average fusiform activation.

Conclusion: Expertise in the attribution of emotion from basic facial expressions was task-dependent in the high-functioning ASD group. The hypothesis that the high-functioning ASD group would be less expert and would have reduced fusiform activation was supported in the perceptual task but not the linguistic task. The reduced fusiform activation in the perceptual task was not explained by reduced expertise; it is therefore concluded that reduced fusiform activation is associated with the diagnosis of ASD.

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Key Words: autism spectrum disorders, emotion, functional magnetic resonance imaging.

(Appendix 2: Publication)

Dedication

The research presented in this thesis was funded by the Roland D. Ciaranello Fellowship in Basic Sciences awarded by National Alliance of Autism Research (NAAR) in 2001. NAAR is a non-profit organisation founded by parents in 1995 to promote and accelerate biomedical research in ASD. The NAAR mission includes funding fellowships and supporting innovative studies that have the potential to yield scientific advances in the autism field. I would like to take this opportunity to thank NAAR for awarding me the Roland D. Ciaranello Fellowship in Basic Science, which afforded me the opportunity to pursue my interest in studying SCI at Stanford University. I would also like to dedicate this thesis to the memory of Roland D. Ciaranello, who founded the Stanford Autism Research Group, of which I was part, and in whose name I was awarded this fellowship.

Foreword

Until recently, one of the young men with ASD who participated in this research had no idea that there was such a thing as social communication. He perceived facial expressions and gestures as meaningless biological by-products, not as the social communication of others. He required to laboriously process the non-verbal social communication of others, immediately understood at a subconscious level by most, at a conscious level, which made every social situation a challenge for him.

During the research, he confided that it was evident to him from an early age that other people were more socially adept. He realised that an innocent facial expression or gesture from him would be misconstrued as rude, whereas, others could make facial expressions or gestures and have everyone creased with laughter. He thought that others must have some kind of 'social lubricant', which initially seemed like a humorous idea, until he spoke sadly of his belief that 'he was actually on the wrong planet'. He described others laughing at him in a social skills training class when he asked if everyone received a manual on how to read faces. Being unable to understand the facial expressions of others, the social world was unpredictable for him and forming relationships stressful and confusing. Despite doing well academically at school, he often told his parents that he would rather live on his own planet to avoid the social world.

This young man, who had marked SCD, was twelve years old when he participated in this research into SCI in ASD. He has an IQ of 132 and is a gifted mathematician with an interest in astrophysics. He does not see his condition as a disability, but rather as another way of being. 'It's like being an Apple computer instead of a PC, which has advantages and disadvantages. I have a different type of operating system that means that I can process some things better, but the problem is that I can't read other people's software!' Despite the disadvantages associated with his SCI, when asked if he would like to be 'neurotypical', he was quite clear that he would not, because he was sure that 'neurotypicals' would be no good at astrophysics!'

The parents of this young man with ASD reported that this group of high functioning young men with SCI were under-researched. This thesis presents an integrated research approach, at the behavioural, cognitive, and functional levels of explanation, focusing on reduced expertise in the attribution of emotion from facial expressions as a potential explanation for the SCI in such high functioning young men.

PART I: INTRODUCTION

Chapter 1 The Categorical and Dimensional Studies

1.1 Introduction to the Categorical and Dimensional Studies

Social communication impairment (SCI) is the core deficit in autism (1, 2) and seen as a dimension of behaviour in individuals with autism spectrum disorders (ASD) (15); however, the aetiology of SCI remains elusive. Previous functional magnetic resonance imaging (fMRI) research has focused on face processing deficits as a possible explanation for the SCI in ASD. Typically developing individuals activate the right fusiform gyrus (FG) during the perceptual processing of human faces, which has been implicated in configural processing and the development of expertise in the processing of face percepts (16). Whereas, individuals with ASD have been reported to use atypical perceptual processing strategies (17) and to have reduced (18) or absent (6) right FG activation when viewing static face stimuli. However, recent fMRI research using static face percepts has reported comparable right FG activation to typically developing individuals when individuals with ASD attended to the eyes region of the face (9) and view the faces of familiar people (10). Consequently, face processing deficits and the associated right FG hypo-activation hypothesis has become a contentious explanation for the SCI seen in autism. Another plausible explanation for SCI in ASD is reduced expertise in the attribution of emotion from facial expressions. Whilst reduced expertise in the attribution of emotion from facial expressions has been acknowledged as a potential explanation for the SCI in autism (1), there has been little research investigating deficits in facial expression processing as an explanation for the SCI in ASD (11). Social communication involves the perceptual, emotion and cognitive processing of the facial gestures of other people to attribute the correct emotion from their facial expressions (2). Emotion attribution from static facial expressions has been shown to activate the FG, amygdala and prefrontal cortex in typically developing individuals associated with perceptual, emotion and cognitive processing respectively (12). Therefore, these three regions of interest (ROI) are potentially informative in terms of the functional aetiology of SCI seen in ASD.

In the initial categorical fMRI study presented in this thesis, neural activation in these three ROI was investigated during the attribution of emotion attribution from static facial expressions. The second categorical fMRI study presented in this thesis investigated if neural activation in the right FG was associated with attention to the eyes region of the face rather than facial expression processing *per se* in individuals with ASD. The first dimensional study presented in this thesis investigates the relationship between SCI and the diagnosis of autism in high functioning young men to determine if those individuals with a diagnosis of autism have greater SCI than those that do not fulfil a diagnosis of autism. The second dimensional fMRI study presented in this thesis further investigated expertise in the attribution of emotion and right FG hyper-responsiveness, which require configural processing and necessitated continuous attention to the face. The dimensional fMRI study also interrogated for an inversion effect during the processing of inverted facial expressions. In the dimensional fMRI study, activation in an additional ROI, the inferior temporal gyrus (ITG) ROI, known to be activated in typically developing individuals during the perceptual processing of inverted face percepts, was also measured during the attribution of emotion from both dynamic non-inverted and inverted facial expressions.

Both categorical and dimensional fMRI studies investigated neural activation in hypothesis-driven anatomical ROI known to be informative in the attribution of emotion from facial expressions in typically developing individuals (12) and explored associations at the functional, cognitive, and behavioural levels of explanation for SCI. The dimensional studies presented in this thesis also explored correlations at the functional, cognitive, and behavioural levels of explanation for SCI. The integration of functional, behavioural and cognitive models of explanation to identify the neurobiological underpinnings of neurodevelopmental disorders has previously been termed 'integrative' research (19). This thesis presents integrative research undertaken to explore the behavioural, cognitive, and functional underpinnings of SCI as seen in ASD.

1.2 Structure of the Categorical and Dimensional Studies

The thesis is broad in scope and, to facilitate coherent presentation, is structured in four parts: Part I, Chapter 1 introduces and outlines the thesis structure then presents the overarching aims, rationale, and hypothesis of the categorical and dimensional studies presented in the thesis. Part I, Chapter 2, presents the methodology used in the categorical and dimensional studies including recruitment, qualitative and quantitative measures, paradigm design and procedure, imaging and statistical analysis methodology.

Part II of this thesis presents the categorical studies, which investigate the association between SCI and emotional attribution from static facial expressions in the FG, amygdala, and prefrontal ROI in young men with ASD and typically developing individuals. Part II, Chapter 3 presents a literature review relating to the categorical studies of emotional attribution from static facial expressions in ASD, and reviews the cognitive and functional constructs previously proposed as potential explanations for the SCI seen in ASD. Part II, Chapters 4 presents Study 1, an fMRI study of the neural activation associated with diagnosis in three hypothesis-driven ROI during the attribution of emotion from static facial expressions in individuals with ASD. Part II, Chapter 5 presents Study 2, an fMRI study of the neural activation, in the ROI identified as associated with an ASD diagnosis in Study 1, during the attribution of gaze direction from neutral faces in individuals with ASD. Part II, Chapter 6 synthesises the categorical studies and presents the conclusions and possible implications of the categorical studies for subsequent studies in the thesis.

Part III of this thesis presents the dimensional studies, which extend and build upon the findings of the categorical studies in Part II by investigating the correlation between SCI and activation in the FG and ITG ROI during the attribution of emotion from dynamic facial expressions in young men with social communication difficulties (SCD) and their relatives. Part III, Chapter 7 gives an overview of the dimensional studies introducing social communication and SCI as dimensions of behaviour, and discussing the levels of investigation required to develop an aetiologically valid integrated explanatory model for the SCI in autism. Part III, Chapter 8 presents Study 3, which investigates the relationship between SCI and the diagnosis of autism in high functioning young men to determine if those with a diagnosis of autism have greater SCI and facilitate comparison of findings across the categorical and dimensional studies presented in this thesis. Part III, Chapter 9 presents Study 4, an event-related fMRI study that investigates the relationship between SCI and neural activation in the FG and ITG ROI during the attribution of emotion from non-inverted and inverted dynamic facial expressions in young men with

SCD and their brothers. Part III, Chapter 10 synthesises the dimensional studies and presents the conclusion and possible implications for the further studies of SCI. For each of the studies presented in Parts II and III there is: a brief introduction giving the literature directly pertinent to that particular study; aims, rationale and hypothesis; methodology; results; data interpretation; key findings; discussion and methodological considerations; and, conclusions with implications for subsequent studies.

Part IV, Chapter 11 discusses: the categorical and dimensional studies; the apparent paradox in terms of the literature on SCI and face/ facial expression processing in ASD; and, further research necessary. Part IV, Chapter 12 presents: the conclusions from the categorical and dimensional studies; and, potential future directions for integrative research.

1.3 Aims of the Categorical and Dimensional Studies

Whilst reduced expertise in the attribution of emotion from facial expressions has been acknowledged as a potential explanation for the SCI in autism (2), there has been no previous research investigating deficits in the attribution of emotion as an explanation for the SCI in high functioning individuals with ASD. The overarching aim of the categorical and dimensional studies presented in this thesis was to determine if reduced expertise in the attribution of emotion from facial expressions represents a plausible explanation for SCI as seen in ASD.

1.4 Rationale of the Categorical and Dimensional Studies

The overarching rationale of the thesis was that reduced expertise in the attribution of emotion from facial expressions offers a plausible explanation for SCI seen in ASD. Emotion attribution from static facial expressions has been shown to activate the FG, amygdala, and prefrontal cortex in typically developing individuals associated with perceptual, emotion and cognitive processing respectively of non-inverted face percepts (15). The ITG has been associated with the perceptual processing of non-inverted face percepts in individuals with ASD (18). Atypical activation in all four of these ROI have been reported in autism; therefore, these four ROI are, potentially, informative in terms of the functional aetiology of SCI and, hence, were the focus of the research presented in this thesis.

1.5 Hypothesis of Categorical and Dimensional Studies

Individuals with SCI would have reduced expertise in the attribution of emotion from both static and dynamic facial expressions.

Reduced expertise in the attribution of emotion from facial expressions in individuals with SCI would, potentially, be related to atypical neural activation in the *a priori* hypothesis-driven ROI, known to be activated during the attribution of emotion in typically developing individuals.

1.6 Methodology Common to the Categorical and Dimensional Studies

To address the aims the categorical and dimensional research studies focused on the neural associations of SCI delineated categorically and dimensionally in individuals with SCD during the attribution of emotion from static and dynamic facial expressions respectively. The common methodologies used to address the aims in the categorical and dimensional studies presented in the thesis are discussed in detail in the next chapter.

Chapter 2 Methodology in the Categorical and Dimensional Studies

2.1 Introduction

Both the categorical and dimensional studies focused on high functioning young men with SCI, as seen in ASD, aged 10-18 years living in Northern California. The categorical studies focused on individuals with SCI as determined by an ASD diagnosis using the Autism Diagnostic Interview-Revised (ADI-R) (20) and the Autism Diagnostic Observation Schedule (ADOS-G) (21) . The dimensional studies focused individuals with SCI measured quantitatively as a dimension of behaviour using the Social Responsivity Scale (SRS) (13). Neural activation was investigated in four hypothesis-driven ROI, FG, prefrontal amygdala, and ITG ROI, which were delineated anatomically, while high functioning young men attributed emotion from static and dynamic facial expressions in the categorical and dimensional fMRI studies.

In brief, the categorical studies recruited 16 high functioning young males between 10-18 years of age with SCI, who had sufficient autistic symptomatology to fulfil criteria for ASD, and 10 typically developing high functioning males. These 26 high functioning young men undertook two block-presentation experimental paradigms while fMRI images were acquired. The Emotion Attribution Paradigm (EAP) required the attribution of emotion from static facial expressions and the Gaze Attribution Paradigm (GAP) required the attribution of gaze direction from neutral faces. ROI analysis focusing on the FG, prefrontal and amygdala was undertaken on the data acquired from the EAP and whole brain analysis (WBA) and FG ROI analysis was undertaken on data acquired during the GAP to address the aims of the categorical studies presented in this thesis. The dimensional studies recruited high functioning young men between the ages of 10-18 years identified as having SCD by their parents. In addition, all the high functioning young men and their first-degree relatives (FDR) had to fulfil inclusion criteria and be willing to participate in an ongoing genetic study of SCI, the specifics of which is beyond the scope of this thesis. In the first dimensional study, 60 young men with SCD were further characterised using two qualitative measures of autistic symptomatology called the Social Communication Questionnaire (SCQ) and the ADI-R to determine if they were above threshold for an ASD diagnosis and if they fulfilled criteria for autism respectively, and severity of SCI compared across diagnostic groups. Of these 60 young men, 14 young men with brothers within 4 years of age were asked to participate in the second dimensional fMRI study. All brother pairs agreed to participate, but four pairs were excluded because of permanent orthodontic braces as these cause substantial signal drop out, which results in unusable MRI scans. Therefore, fMRI images were acquired from 10 brother pairs while performing an event-related paradigm called the Dynamic Facial Expression Paradigm (DFEP). This newly developed paradigm required the attribution of emotion from both non-inverted and inverted dynamic facial expressions. ROI analysis focusing on the FG and ITG ROI was undertaken on the data acquired during the DFEP to address the aims of the dimensional fMRI study presented in this thesis.

Recruitment, behavioural measures, demographic and neuropsychological measures, paradigm design and procedure, imaging methodology and statistical analysis are discussed in the following sub-sections.

2.2 Recruitment

2.2.1 Ascertainment

Both the categorical and dimensional studies focused on high functioning young men with SCI, as seen in ASD, who were between 10-18 years of age. The categorical studies focused on individuals with high functioning autism (HFA) and Asperger's Syndrome (AS) as these categories of ASD have specific inclusion criteria. Therefore, the recruitment flier for the categorical studies emphasised an autism or AS diagnosis as inclusion criteria. The dimensional studies focused on SCI, as seen in individuals with ASD, but also seen in other neurodevelopmental disorders such as individuals with NLD and individuals with SCD in the general population. The recruitment flier for the dimensional studies stated that the study was interested in recruiting high functioning young men with SCD, as seen in autism, AS, PDD-NOS, NLD, other neurodevelopmental disorders, and individuals with or without a diagnosis in Northern California. The flier emphasised that recruitment into the study was irrespective of diagnosis and that both those with and without a diagnosis of ASD, who had SCD, were eligible to participate in the study.

Both the categorical and dimensional studies ascertained individuals through: the Stanford ASD Clinic; professionals working with high functioning individuals with SCD in the local community; parent support networks for young people with SCD; through media advertisement; and, study recruitment fliers. Advertisements were also posted: on university websites, such as the Stanford University Department of Neuroimaging website; on websites that provide information for young people with SCD in the community; and, on websites for professionals working with young people with SCD. In the categorical fMRI studies, control individuals were also recruited through media and website-based advertisements. In the dimensional fMRI studies, high functioning young men with brothers within 4 years of age were ascertained from families that had already agreed to participate in the ongoing genetic study of SCI at Stanford University and brothers recruited as related controls.

2.2.2 Inclusion/ Exclusion Criteria

In both the categorical and dimensional studies, individuals who did not have English as their first language were excluded. Individuals with ferrous metal implants or orthodontic braces were excluded from participation in all fMRI experiments as both affect acquisition of complete brain scans. In both the categorical and dimensional studies young men with normal intelligence and general function ability were recruited to facilitate the study of SCI in isolation from deficits in intellectual functioning. Young men with a history of delayed speech, whom had normal language at the time of the study, were not excluded from either the categorical or the dimensional study. High functioning individuals with ASD and anxiety, learning disorder or attention deficit hyperactivity disorder (ADHD), and individuals on medication for these disorders were included in both the categorical and dimensional studies. Individuals with a known neurogenetic aetiology for their ASD (e.g., fragile X or tuberous sclerosis) were excluded from the both studies.

In the categorical studies, all recruited individuals had: a documented clinical diagnosis of HFA or AS; were aged between 10-18 years; had an IQ of greater than 70; and, lived in Northern California. Control individuals aged between 10-18 years with an IQ of greater than 70 were included in the categorical

studies if they had anxiety or attention deficit disorder, and if they were on medication for these symptoms. Control individuals with major psychiatric or neurological disorder were excluded from the categorical studies.

For the dimensional studies, high functioning young men with SCD (probands) and their FDR were recruited if they: had a score of greater than 60 on the SRS; were aged between 10-18 yrs; had an IQ of greater than 70; fulfilled criteria for participation in the ongoing genetic study of SCI; and, lived in Northern California. Inclusion criteria for this genetic study included: the participation of both biological parents, or one biological parent and a biological sibling aged 10 years and older with an IQ greater than 70. Participation in the genetic study required a willingness on the part of the proband and the FDR to undertake cognitive testing and have venous blood drawn for DNA extraction. FDR with psychiatric and developmental difficulties were included irrespective of medication status in the dimensional studies.

2.2.3 Recruitment Procedure

All recruitment procedures described were approved by the Human Subjects Committee at Stanford University School of Medicine. Informed consent was obtained from all subjects and their parents prior to review of the screening packet and again prior to their participation in the individual studies.

In the categorical studies, subjects interested in participating contacted the Neuroimaging Laboratory Recruitment Hotline. If they lived in Northern California, a screening packet, including the SCQ, a study flier and study information brochure, demographic, medical, and psychiatric questionnaire, and consent form for review of the returned information, was sent to their homes. On review of the screening packet, if individuals between 10-18 years had a documented clinical diagnosis of HFA or AS and had an IQ of greater than 70, they were invited to attend the Department of Psychiatry and Bio-behavioural Sciences for further assessment. This assessment included the Wechsler Abbreviated Intelligence Scale (WAIS), which was administered by a fully trained assessor to determine intelligence. The ADI-R and the ADOS-G instruments were also administered to determine a research diagnosis. Two assessors, who had obtained research reliability during formal training with the instrument, administered the ADI-R to the parent(s) of the high functioning young men. Inter-rater reliability was conducted on one third of ADI-R assessments performed and the assessors had an inter-rater agreement of 100% for diagnosis. One trained assessor, who had obtained research reliability during formal training with the ADOS-G, administered the appropriate module of the instrument to all the participants in the categorical study. Individuals who fulfilled criteria for autism, using the ADI-R and/ or criteria for the broader ASD using the ADOS-G, in addition to the other inclusion criteria were recruited.

In the dimensional studies, families interested in participating contacted the Neuroimaging Laboratory Recruitment Hotline. If families lived in Northern California a screening packet including a SCQ, a study flier and study information brochure, demographic, medical and psychiatric questionnaire, and consent form giving consent for review of the returned information was sent to their homes. Young men with SCD (and their FDR) were recruited if the young men: had a score of greater than 60 on the SRS; were aged between 10-18 yrs; had an IQ of greater than 70; and, also fulfilled inclusion criteria for participation in the ongoing genetic study of SCI. The parents of these young men also had to be willing

to undertaken the ADI-R to allow further diagnostic assessment. One assessor, who had obtained research reliability during formal training, administered the ADI-R to the parent in the young person's home. The ADOS-G was not administered in the dimensional studies; however, an expert in the clinical diagnosis of ASD interviewed all participants in order to ensure that they met study criteria.

2.3 Behavioural Measures

The categorical studies used the SCQ to screen for individuals with sufficient autistic symptoms to be above the screening threshold for a diagnosis of autism. The ADI-R (20) and the ADOS-G (21) were then undertaken to ensure that the individuals fulfilled research criteria for a diagnosis of ASD and determine which individuals attracted a diagnosis of autism. These categorical (or qualitative) diagnostic measures are considered the 'gold standards' in the diagnosis of autism for the purposes of research. The dimensional studies used the SRS to quantify SCI in individuals with SCD. The discriminant validity of this quantitative measure has previously been reported for individuals with an ADI-R diagnosis of autism (22); however, the ADI-R was also undertaken to determine if the individuals had sufficient SCI to fulfil the social domain of the ADI-R and determine if they fulfilled full criteria for a diagnosis of autism (20). The qualitative and quantative behavioural measures used are described in detail in the following sub-sections.

2.3.1 Social Communication Questionnaire

The SCQ (23), previously known as the Autism Screening Questionnaire, is a 40 item parent-report screening questionnaire, which categorically ascertains autistic symptoms. The SCQ is considered a reliable and valid qualitative screening instrument for PDD (20). The SCQ covers the same areas of functioning as the ADI-R (social interaction, language and communication and repetitive stereotyped patterns of behaviours), but in a much briefer format. The SCQ is also consistent with the International Classification of Disease-10 (ICD-10) (24) and Diagnostic Statistical Manual-IV (DSM-IV) (25) criteria for the diagnosis of autism. The SCQ focuses on qualitative deviance between four to five years of age. A score of 15 or above provides the best discriminative validity between ASD and non-ASD diagnosis (23) and was used as the cut-off in the categorical studies.

2.3.2 Autism Diagnostic Interview-Revised

The ADI-R is the most commonly used instrument to establish a diagnosis of autism in research settings, and is a clinician administered (investigator-based), 111-item semi-structured, interview undertaken with the parent of the individual suspected of having an autism diagnosis. The ADI-R has predetermined questions (probes) and codes for each behavioural item. The diagnostic decision is based on whether the behavioural description given by the parent is adequate for a coding and not on whether all the probes have been used. If the coding remains in doubt, the interviewer considers which probes would help resolve the doubts, and asks them accordingly. Diagnostic codes have been devised with the aim of differentiating developmental delay or impairment in some function, from deviance, or qualitative abnormality in that function. The investigator-based interview relies heavily on skilled interviewing techniques to elicit a detailed description of actual behaviours. The interviewer must be trained in the use of the instrument, and have a detailed knowledge of the conceptual distinctions involved in each

coding. To ensure this, interviewers must undertake research training, and obtain research reliability with others trained in the use of the interview for research purposes, prior to using the instrument to diagnose ASD.

The ADI-R primarily focuses on the key diagnostic characteristics specified in ICD-10 and DSM-IV, namely, those features concerned with developmental delays and deviance in reciprocal social interaction, language, communication and play, and restricted repetitive stereotyped behaviours and interests. The ADI-R items considered by the developers to best exemplify DSM-IV and ICD-10 criteria for autism are included in the scoring algorithm, which is intended to allow the rater to make a categorical diagnosis of autism. The ADI-R generates algorithm scores for the three sub-domains of autistic symptomatology: qualitative impairments in reciprocal social behaviour; communication; and, repetitive behaviours and stereotyped patterns of behaviour. The ADI-R scores are recorded for behaviours in two periods - behaviours between the ages of 4 and 5 years (most abnormal) and current behaviours (within the last three months). The items that best discriminate autism are used in the scoring algorithm to generate a most abnormal and a current functioning ADI-R score. The interviewer rates each assessed behaviour on the ADI-R based on the parent's response ranging from 0 for normal to 3 for very abnormal. To meet ADI-R criteria for autism an individual must meet the threshold algorithm score in each of the three sub-domain and exhibit an abnormality in at least one sub-domain by 36 months of age.

2.3.2.1 Autism Diagnostic Schedule-Generic

The ADOS-G is a semi-structured, standardised assessment of social interaction, communication, play, and imaginative use of materials for individuals suspected of having ASD. The observational schedule consists of four 30-minute modules, each designed for administration to different groups of individuals according to their level of expressive language - ranging from no expressive or receptive language to verbally fluent adults. Each module consists of standard activities that allow the examiner to observe the occurrence (or non-occurrence) of behaviours that have been identified as important to the diagnosis of autism and other ASD across developmental levels and chronological ages. Structured activities and materials, and less structured interactions, provide standard contexts in which social, communicative and other behaviours relevant to ASD are observed. Again, individuals who administer the instrument require to be trained in administering the instrument, understand the concepts inherent in the modules and obtain research reliability with others trained in the use of the instrument for research.

Within each module, the participant's response to each activity is recorded and overall ratings made at the end of the schedule. These ratings can then be used to formulate a diagnosis using a diagnostic algorithm for each module. The diagnostic algorithms sensitivity and specificity for autism and pervasive developmental disorder - not otherwise specified (PDD-NOS), relative to non-spectrum disorders, has been reported as excellent with moderate differentiation of autism from PDD-NOS. Module 1 is intended for individuals who do not consistently use phrase speech and Module 2 for individuals with some phrase speech who are not verbally fluent. Module 3 is intended for verbally fluent children and adolescents for whom playing with toys is still age-appropriate. Module 4, which was the predominant

module used in the presented research, is intended for verbally fluent groups of adolescents for whom playing with toys is not age-appropriate. Modules 3 and 4 were both used to diagnosis the verbally fluent young men recruited for the categorical and dimensional studies, depending on whether play was still appropriate. The activities in these modules overlap, and range from having a focus on interactive and make-believe play in Module 3 to focusing on conversation about social relationships at school or work in Module 4. Module 4 also includes socio-emotional questions and some interview items about daily living skills. In effect, each module of the ADOS-G provides a 30-45 minute observation period during which the examiner presents the individual being assessed with numerous opportunities to exhibit behaviours of interest in the diagnosis of autism/ ASD through standard 'presses' for communication and social interaction. Within each module, there is substantial inter-rater and test-retest reliability for individual items, excellent inter-rater reliability within domains and excellent internal consistency.

2.3.2.2 Social Responsivity Scale

The SRS, formerly known as the Social Reciprocity Scale, is a 65 item screening questionnaire that can rapidly (15-20 minutes) and reliably measure the impairments in social behaviour typically seen in autism as a quantitative trait across a range of severity and PDD disorders, including AS and PDD-NOS (14). The SRS is completed by an adult, who has observed the individual in a naturalistic social setting, and ascertains autistic symptoms observed over the past six months across the range of autistic symptom severity as a quantitative trait. The score varies from 1 to 195, based on a 0 to 3 weighting given to each of the 65 question responses. The SRS questions can be divided into five treatment subscales: (i.) Social Awareness (8 questions) - such as ability to notice social cues. The items in this category represent the sensory aspects of reciprocal social behaviour. (ii.) Social Information Processing (12 questions) - such as ability to interpret social cues once they are picked up. The items in this category represent the cognitive-interpretive aspects of reciprocal social behaviour. (iii.) Social Responses (22 questions) - which includes questions on expressive social communication and represents the 'motoric' aspects of reciprocal social behaviour. (iv.) Social Motivation (11 questions) - which includes questions on the extent to which a subject is generally motivated to engage in social-interpersonal behaviour including questions which focus on social anxiety, inhibition and empathic orientation. (iv.) Preoccupations or mannerisms (12 questions) - includes questions on stereotypic behaviours or highly restricted interests characteristic of autism (13).

The psychometric properties of the SRS have been described from studies which collectively have involved 2000 children from the general population aged 4-18 yrs (15). The SRS is capable of distinguishing children with pervasive developmental disorders (PDD) from those with other psychiatric disorders and has been shown to measure the same constructs as ascertained by the ADI-R (22). Previous studies support that the interview can be completed by an adult, who routinely observes the individual and their social interaction with others, and that there is a strong correlation between maternal and paternal scores ($r = 0.91$). In this thesis, the notion of SRS completion by an adult that routinely observes the individual and their social interaction is extended to include the use of the SRS as a spouse report. A SRS raw score above 70 is recommended for the purpose of screening for any of the ASD (Autistic Disorder, atypical autism or PDD-NOS, AS) in boys in school or other general population

groups and results in sensitivity of 0.77 and specificity of 0.75 for an ADI-R diagnosis of autism. The SRS has been shown to be highly correlated (0.65, 0.63, 0.77) with all three sub-domains of the ADI-R. In this study of individuals with ASD, subjects with an ADI-R score above the clinical cut-off for an ADI-R diagnosis of autism all had an SRS raw score above 65 (22). Deficits across all three sub-domains are characterised by general impairment in reciprocal social behaviour for which the SRS generates a single index SRS score (14). The factor structure of the SRS is discussed later in the thesis.

2.4 Demographic and Neuropsychological Measures

2.4.1 Demographic, Medical and Psychiatric Questionnaire

The demographic, medical, and psychiatric questionnaire posed questions to determine the ethnicity of the high functioning individual with ASD and the socio-economic status of the family. The questionnaire also screened for medical disorders and any co-morbid neurodevelopmental or neuropsychiatric conditions in the high functioning young men. The questionnaire also asked about past and present medication and for any history of ferrous metal implants/ dentistry that would affect scan acquisition. The Edinburgh Handedness Inventory (EHI) was included in the questionnaire to determine handedness of potential participants in the fMRI studies. To determine handedness the EHI asks participants to indicate their preferred use of hand in the following activities: writing, drawing, throwing, using - scissors, - toothbrush, - knife (without fork), - spoon, - broom (upper hand), striking a match, opening a box lid, or to denote either hand if they had no preference. Scores of: 33-36 = strongly right-handed (RH); 29-32 = moderately RH; 25-28 = weakly RH; 24 = ambidextrous; 20-23 = weakly left-handed (LH); 16-19 = moderately LH; 12-15 = strongly LH.

2.4.2 Neuropsychological Measures

Two verbal and two performance subtests from the Wechsler Abbreviate Intelligence Scales (WAIS) were used to estimate full scale IQ (FSIQ), verbal IQ (VIQ), and performance IQ (PIQ) respectively. WAIS is nationally standardised and yields the three traditional VIQ, PIQ, and FSIQ scores. It is also related to the Wechsler Intelligence Scale for Children-Third Edition (WISC–III) and the Wechsler Adult Intelligence Scale-Third Edition (WAIS–III). The WAIS consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. The Vocabulary (providing definitions of words) and Similarities (identifying the way in which two things are alike) subtests compose the Verbal Scale and yield the VIQ. The PIQ score is generated from two different types of performance measure - Matrix Reasoning (identifying the logical addition to a matrix pattern from one of four choices), which measures non-verbal fluid abilities and Block Design (time to assemble patterned blocks to replicate given pattern), which measures visiomotor/ coordination skills. VIQ and PIQ scores were estimated by pro-rating sums of scaled scores based on the two subtests for each scale. The WAIS was chosen because it is a nationally standardised reliable brief measure of IQ, which can be administered to individuals 6-89 years of age in approximately 30 minutes, and generates VIQ and PIQ, as well as FSIQ, scores.

2.5 Paradigm Design and Procedure

In the categorical studies, the participants performed the EAP and the GAP and in the dimensional study, participants performed the DFEP. Accuracy and response time were measured as indicators of expertise

in all paradigms that investigated the attribution of emotion from facial expressions and as an indication of attention in the GAP. Paradigm design and procedure is described for all three paradigms in the following sub-sections.

2.5.1 Emotion Attribution Paradigm

The EAP consisted of three tasks the emotion match (EM) (perceptual) task, the emotion label (EL) (linguistic) task, and the control task. In the EM task (Figure 2-1 A), the subjects matched the facial expression presented on a target face with the same facial expression present on one of two other faces simultaneously presented below. In the EL task (Figure 2-1 B), the subjects matched the facial expression presented on the target face with one of two affective labels presented below.

A standard set of 18 pictures was used for the experimental tasks and included photographs of faces with fearful, surprised, and angry facial expressions.

Figure 2-1 Emotion Attribution Paradigm

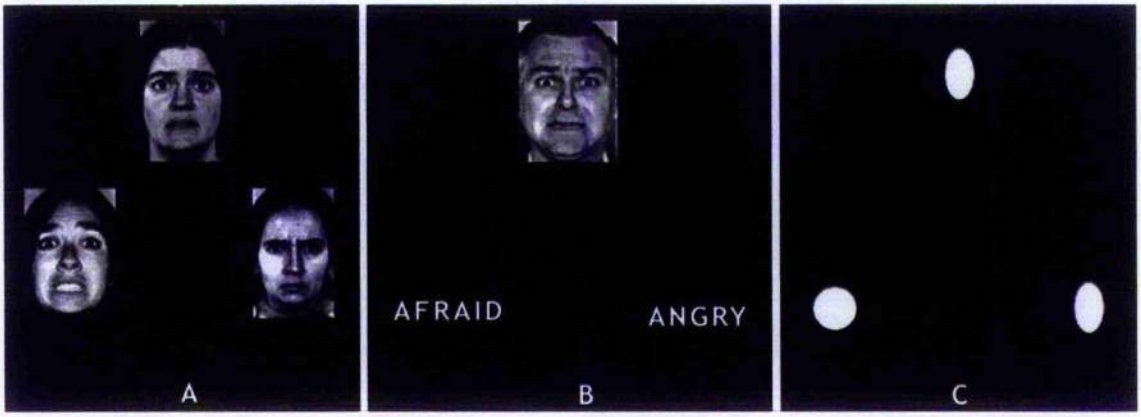


Figure 2-1 shows an example of stimuli used in each of the tasks: (A) the emotion match (EM) task; (B) the emotion label (EL) task; and, (C) the control task in the Emotion Attribution Paradigm.

In the control task (Figure 2-1 C), the subjects matched one of six oval target forms to one of two oval forms presented simultaneously below (26). Oval target forms were used to control for cognitive processes involved in the visual processing of three percepts. Neutral faces were not used in the control task as adolescents have been shown to attribute emotional salience to neutral faces (27). Each subject performed all three tasks as part of the EAP.

The experiment consisted of nine blocks: five blocks of control task alternated with four alternating experimental blocks (two blocks of the EM task and two blocks of the EL task). The task consisted of rest, instructions-experimental (EM or EL) or control blocks in the following order: rest-instructions-control-EM-control-EL-control-EM-control-EL-control-'good job'-rest. Six face photographs were presented in a random order within each block for five seconds each. Each 30-second experimental block (EL and EM) was presented twice and a 30-second control block presented five times alternating

with the experimental tasks. Six oval forms were presented in a random order within block for five seconds each.

The scan started and ended with a 30.5-second rest period. Each of the nine blocks was prefixed by a 2.5-second instruction set. Nine 32.5-second blocks and two 30.5-second rest periods were presented equating to a total scan time of 5 minutes 52.5 seconds. Accuracy and response time were measured during the EAP as an indication of expertise in the attribution of emotion from static facial expressions.

2.5.2 Gaze Attribution Paradigm

Individuals were instructed to attend to the eyes region of emotionally neutral faces, and to identify the direction of gaze from one of four types of presentation in the GAP (Figure 2-2): face forward-gaze forward; face forward-gaze angled; face angled-gaze forward; and, face angled-gaze angled.

Figure 2-2 Gaze Attribution Paradigm

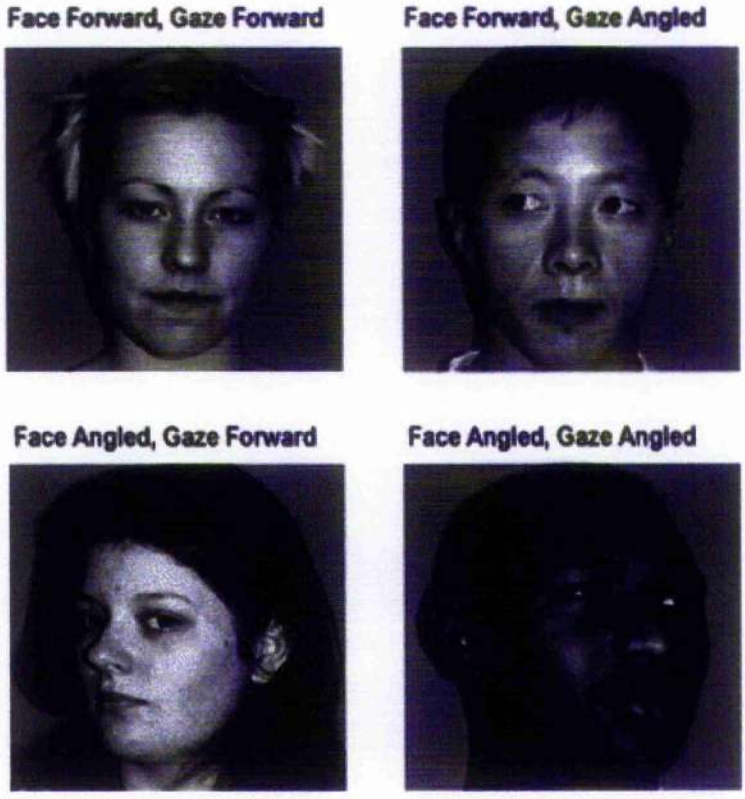


Figure 2-2 shows experimental tasks: face forward-gaze forward; face forward-gaze angled; face angled-gaze forward; and, face angled-gaze angled tasks in the Gaze Attribution Paradigm.

Each individual was required to press a response pad using his right forefinger for gaze forward and his right middle finger for gaze angled. In the control task, the subjects pressed alternating buttons once as they viewed each of the scrambled faces to control for brain activation related to button response.

The experimental stimuli consisted of 60 unique static pictures of emotionally neutral faces and 60 isoluminant scrambled faces. The face pictures were acquired with a digital camera against a common background with a view angle of 20 degrees at 2 metres. The experiment consisted of six blocks - three experimental blocks alternated with three blocks of control task.

Each experimental block contained 20 face presentations. The four types of face presentation were presented in a random order for 1750 millisecond (msec) each with a 250 msec inter-stimulus interval (ISI). In the control block, 20 scrambled face presentations were presented for 1750 msec each with a 250 msec ISI. The scan started and ended with a 30-second rest period and six 40-second blocks were presented equating to a total scan time of 5 minutes.

Subject response time was recorded for two seconds from the beginning of each presentation until the end of the 250 msec ISI. Correct and incorrect responses and response times were recorded if they occurred between 150 and 2000 msec after the stimulus. The number of pictures in which the face and gaze were angled to the right was balanced with the number of pictures in which the face and gaze were angled to the left. To avoid repetition effects, no picture was presented twice. Accuracy and response time were measured as an indication of attention to the eyes region of the neutral face stimuli.

2.5.3 Dynamic Facial Expression Paradigm

Thirty photographs of actor's faces (15 female and 15 male) from a standardised digital database of facial expressions were used. This database was developed by Gur and colleagues (28) and these stimuli were used with the permission of the developers in the DFEP.

The DFEP incorporated 90 movies of faces produced from photographs of 15 male and 15 female actors depicting happy, neutral, and sad facial expressions. Two-dimensional colour photographs of intense happy, intense unhappy and neutral facial expressions were selected for each actor.

These three colour photographs, which had been obtained under standardised conditions, had previously had the expressed facial emotion validated. These photographs were centred in oval black frames and 30 neutral to happy, 30 neutral to unhappy and 30 neutral to neutral 'movies' made using Morphman Software (29). These non-inverted (upright) movies morphed over a 10 second period at a rate of 24 frames/ second and were inverted using Back to Black software (30) to create an equivalent number of inverted movies.

The DFEP incorporated: 30 movies of neutral facial expressions that changed to become happy facial expressions (Figure 2-3); 30 movies of neutral facial expressions that changed to become unhappy facial expressions (Figure 2-4); and, 30 movies of neutral facial expressions that remained as neutral facial expressions.

Figure 2-3 Non-inverted Condition Dynamic Facial Expression Paradigm

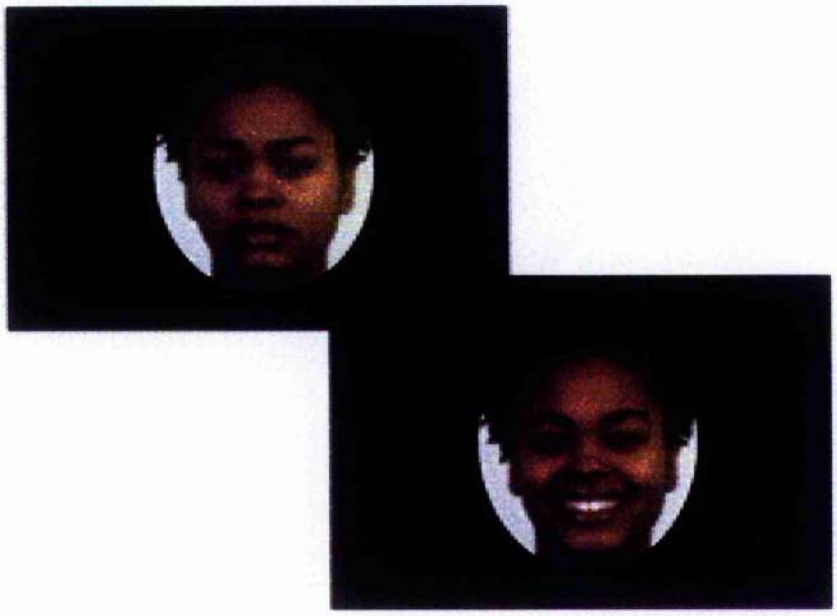


Figure 2-3 shows an example of the stimuli morphed in the non-inverted task to produce a neutral to happy facial expression movie for the Dynamic Facial Expression Paradigm.

Figure 2-4 Inverted Condition Dynamic Facial Expression Paradigm

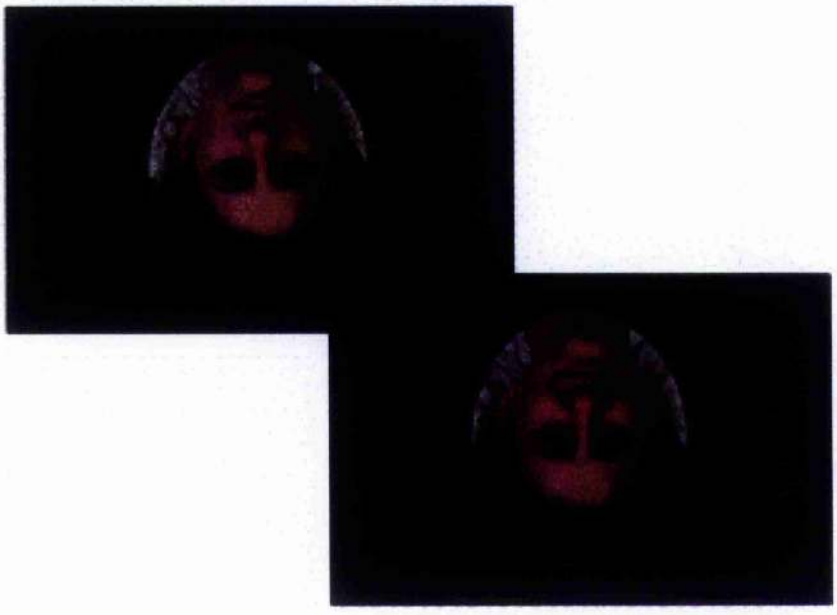


Figure 2-4 shows an example of the stimuli morphed in the inverted task to produce an inverted neutral to unhappy facial expression movie for the Dynamic Facial Expression Paradigm.

All movies contained a similar amount of movement including the neutral movies to match for the movement inherent in the experimental conditions of the DFEP and provide a control condition for the experimental conditions of the DFEP.

In the DFEP the experimental task consisted of three runs each of which had 30 stimuli: 5 happy non-inverted; 5 happy inverted; 5 unhappy non-inverted; 5 unhappy inverted; 5 neutral non-inverted; and, 5 neutral inverted. The stimuli onsets were jittered and the average ISI was 10 seconds (8, 10, and 12 sec). The different conditions were counterbalanced (non-inverted/ inverted; female/ male; happy/ unhappy/ neutral), and the order of presentation pseudo-randomised in each run using presentation optimisation software tool called OPTSEQ (http://surfer.nmr.mgh.harvard.edu/optseq). The total scan time equated to 11.06 minutes including a 20-second rest period at the beginning and a 40-second rest period at the end of each scan.

The DFEP was programmed on a Macintosh G4 Notebook using PsyScope experimental presentation software (31) and the movies were supported using QuickTime 6 (32). The DFEP was synchronised with the scan using a TTL pulse delivered to the scanner. Stimuli were presented visually at the centre of a screen using a custom-built Resonance Technology magnet-compatible projection system.

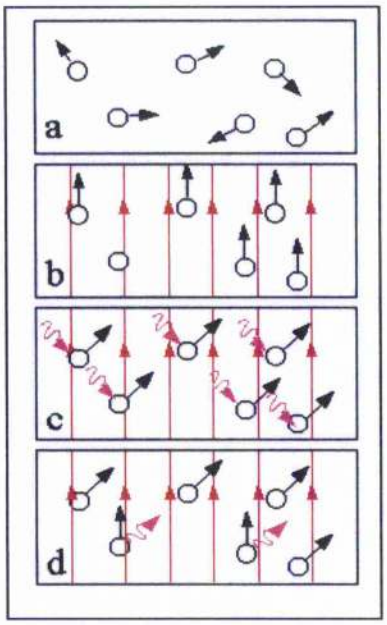
Subjects were trained on a practice version of the DFEP prior to the scan, which did not use the same stimuli, to ensure that they understood the paradigm and were capable of attending to and performing the DFEP in the scanner. During the actual scan, each run was prefixed by an instruction set that stated that the individuals would see faces that would become happy or become unhappy. The subject was instructed to: press button 1 using their first finger if the face was becoming happy; to press button 2 using their second finger if the face was becoming unhappy; and, to press button 3 using their third finger if the face remained neutral as 'soon as they were sure'.

During the DFEP, accuracy and response time were recorded as an indicator of expertise in the attribution of emotion from dynamic facial expressions. During the ISI, the participants were presented with a blank screen and the DFEP ended in a screen that said 'Good Job'.

2.6 Imaging Methods

The advent of magnetic resonance imaging (MRI) technology offers the opportunity to non-invasively measure brain structure and activation in studies of neurodevelopmental disorder. In this section, the process of MRI is first explained and the explanation then expanded to fMRI. The fMRI simulation and behavioural desensitisation techniques that were used across the categorical and dimensional studies are described. FMRI acquisition in block and event-related experimental designs and anatomical circumscription of the four hypothesis-driven ROI are also explained.

2.6.1 Magnetic Resonance Imaging



MRI generates cross-sectional images of the human body by using nuclear magnetic resonance (NMR). (a.) The process begins with positioning the individual in the scanner. (b.) Then a strong, uniform magnetic field, which polarises water protons by forcing their spins into one of two possible orientations, is applied. (c.). Next an appropriately polarised radio-frequency field, applied at resonant frequency, forces spin transitions between the two orientations. (d.) This creates a signal that can be detected by a receiving coil. The quality of this signal is determined by the signal noise ratio (SNR). SNR is optimised for each scan by measuring and refining SNR parameters.

An MRI scanner applies pulses of radio-frequency energy that only excites protons whose resonant frequencies fall within a narrow range. Applying magnetic field gradients during the pulse creates resonant conditions for only the protons that are located in a thin, predetermined slice of the body. Orientation and thickness of this slice can be selected arbitrarily in the imaged body. The NMR signal encodes positional information across the slice by using a method known as "spin warp" and two-dimensional "Fourier Transformation" extracts the positional information. The process creates a data matrix in which each element represents an NMR signal from a single, localised voxel within the imaged slice. A two dimensional display of this matrix's contents creates an image of the selected slice. Each image element or pixel represents the NMR signal strength that was recorded for the corresponding voxel in the anatomical image.

2.6.2 Functional Magnetic Resonance Imaging

The advent of fMRI extends traditional anatomical imaging to allow for the production of maps of human brain function. FMRI is based on the increase in blood flow that accompanies neural activity in the brain. The increase in blood flow results in a corresponding local reduction in deoxyhaemoglobin. Since deoxyhaemoglobin is paramagnetic, it alters the T2* weighted MRI signal (33, 34). Thus, deoxyhaemoglobin, which is sometimes referred to as an endogenous contrast-enhancing agent, serves as the source of the signal for fMRI. Using an appropriate imaging sequence, human brain functions can be observed without the use of exogenous contrasts (35). When compared with other medical-imaging techniques, fMRI provides several significant advantages: it is non-invasive; uses non-ionizing radiation and is, therefore, safe; and, gives excellent soft tissue contrast.

FMRI provides a high resolution, non-invasive technique to detect neural activity by measurement of the blood oxygen level dependent (BOLD) signal (33, 34) and has the potential to provide novel insights into the nature of normal and abnormal brain function in neurodevelopmental disorders. Indeed, this methodology can be used to map changes in brain haemodynamics that correspond to cognitive constructs. The advent of fMRI is poised to further inform our theoretical conceptions of

neurodevelopmental disorders, and facilitate research to determine the underlying aetiologies for complex neurodevelopmental disorders (36). However, acquisition of fMRI data from populations with neurodevelopmental disorders such as autism, are associated with a number of methodological challenges. Individuals with neurodevelopmental disorders are hard to ascertain, therefore, preliminary fMRI studies on small sample sizes often focus on ROI analysis, a statistically conservative methodology that affords greater power within the degrees of freedom afforded by small sample sizes. Individuals with neurodevelopmental disorders also need to be able to give informed consent and be able to comply with the requirement to remain still and noise in the fMRI environment. These challenges have resulted in individuals from these populations, particularly young or less cognitively able individuals, being less intensively studied using fMRI. However, neurodevelopmental disorders are actually of great interest because of the atypical neurodevelopment and preponderance of atypical information processing strategies in these populations. Fortunately, the collection of good quality fMRI data is achievable in neurodevelopmental disorder through the ascertainment of high functioning individuals, and the use of behavioural desensitisation and fMRI simulation techniques (37).

2.6.3 Functional Magnetic Resonance Imaging Simulation

Before each study presented in this thesis, participants undertook a behavioural desensitisation program, which involved listening to the fMRI scanner noises on a CD and watching a movie called the "Stanford FMRI Experience" at home. Participants were asked to practice remaining still and given the instructions for a game that encouraged this called the "Statue Game." Participants also undertook fMRI simulation to reduce anxiety; and, ensure that the individuals had the ability to perform the respective experiments. The fMRI simulator allows participants to further desensitise to the high noise/ low space fMRI environment and the simulated fMRI 'experience' allows the investigator to achieve informed consent from the research participant for the actual fMRI scan. The fMRI simulator used in the studies presented in this thesis looked and sounded like the actual fMRI scanner used, but was fitted with a mock head coil. During fMRI experiments, participants are required to remain as still as possible to allow the successful acquisition of fMRI data. The fMRI simulator allows for behavioural training in the fMRI environment to reduced head movement and increase compliance during fMRI data acquisition. Often participants are not aware of head movement, especially movement that occurs in the vertical axis, associated with respiration. The fMRI simulator is of particular benefit with young people, who have been reported to have greater head motion than adults, as this movement responds to progressive fMRI simulation techniques designed to reduce head motion (38).

The fMRI simulator technique involves the use of a projector to display the participant's favourite DVD movie/ cartoon onto a projection screen, which the participant views via a mirror built into the head coil. The head motion sensor and motion detector software give the participant 'bio-feedback' in three-dimensional space (x, y, z). Head movement above a specified threshold results in their chosen movie pausing until head movement returns to below the set threshold. Over the course of training, the head movement threshold is reduced, leading to increased participant awareness and progressive reduction in head movement. This technique is effective in modifying the behaviour of participants and increasing the successful acquisition of fMRI data.

Prior to the experiments, the individual participants also performed 'practice' dexterity tasks in the fMRI simulator. Button presses were presented on the projection screen using experiment presentation software. A response device, essentially a handheld pad with buttons that is at the participant's side when in the scanner, allowed the participant to practice responding using the appropriate fingers for button presses. These buttons are out of the participant's field of vision when in the scanner. If button presses are not practiced in the mock scanner this can be problematic during the actual scan as fingers can easily become misplaced on the button pad. During the practice dexterity task, participants were also trained not to look to at their fingers to reduce head movement. Instead experiment presentation software in the fMRI simulator gives the participant visual feedback via mirrors mounted on the head coil. This helps the participant to establish a 'feel' for the response device reducing the chance of erroneous responses and head movement during the actual scan.

The participants also had the opportunity to perform 'practice' versions of the paradigms that were to be presented in the actual scanner to ensure that they understood the paradigm requirements and could achieve adequate performance. Ensuring adequate performance is of importance for the accurate interpretation of fMRI results and comparable performance actually necessary to allow comparison of neural activation between groups (39). The fMRI simulator provided the opportunity to emphasise fMRI safety related information to participants and, ultimately, improved the participant experience in the fMRI environment. This further facilitated the successful acquisition of fMRI data from these high functioning individuals with ASD in the categorical and dimensional studies presented in this thesis.

2.6.4 Functional Magnetic Resonance Imaging Acquisition

In both the categorical and dimensional studies, the initiation of data acquisition and the initiation of the paradigm were synchronised using a TTL pulse delivered to the scanner timing microprocessor board from a 'CMU Button Box' microprocessor. This 'CMU Button Box' microprocessor was connected to the Macintosh computer running the PsyScope paradigm presentation software. The paradigms in the categorical fMRI studies were presented using a block experimental design and the fMRI paradigm presented in the dimensional study was presented using an event-related experimental design. The block and event-related experimental designs and associated acquisitions parameters for the categorical and dimensional studies, although different, are related and, therefore, discussed in the following sub-sections.

2.6.4.1 Block Design

In the categorical studies, the advent of fMRI allowed for the non-invasive investigation of the neural associations of SCI during the attribution of emotion from static facial expressions in individuals with ASD. The categorical studies presented the experimental and control stimuli in the EAP and GAP in a block design. Block design is the most efficient way of presenting short stimuli as fMRI signal can be rapidly accumulated based on General Linear Model (GLM) assumptions relating to the haemodynamic response function (HRF). However, block design paradigms do not allow for the removal of signal generated by inaccurate responses to experimental or control stimuli.

For the block designs used in the EAP and the GAP, the structural and functional MRI data was acquired on a 3T GE Signs scanner using a standard GE whole head coil. A custom-built head stabilisation system prevented head movement. The entire brain was imaged in 28 axial slices parallel to the anterior commissure-posterior commissure (AC-PC) line. These slices were 4 mm thick with a 0.5 mm skip between slices. A shimming procedure was used before acquiring fMRI scans (40) using a T2* weighted gradient echo spiral pulse sequence [Time to Response (TR) = 200 msec; Time to Echo (TE) = 30 msec; Flip Angle (FA) = 89° and 1 interleave; Field of View (FOV) = 200 x 200 mm²; Matrix = 64 x 64, In-plane Resolution = 3.125 mm] (41). A high-resolution 124 slice T1-weighted 3D spoiled gradient recalled (SPGR) anatomical image was acquired during the same scan session in the sagittal plane (TR = 35 msec; TE = 6 msec; FA = 45°; 24 cm FOV; 256 x 192 matrix and acquired resolution = 1.5 x 0.9 x 1.2 mm).

2.6.4.2 Event-Related Design

In the dimensional studies, an event-related fMRI design allowed for the investigation of the neural correlates of SCI during the attribution of emotion from dynamic facial expressions in individuals with ASD. Although an event-related design presentation does allow for the removal of signal generated by inaccurate responses to stimuli, this design is an inefficient way of presenting static stimuli. To generate a detectable signal inter-stimulus intervals (ISI) need to be either: sufficiently long to allow the HRF to return to baseline, which makes it difficult to present sufficient stimuli to obtain a detectable signal in any experimental run; or, the stimuli need to be expertly counter-balanced to fulfil GLM assumptions, and then rapidly presented pseudo-randomly overlapping with each other. The dimensional fMRI studies presented the experimental and control stimuli in the later fashion in a rapid event-related design to generate sufficient signal from the DFEP for analysis.

The event-related images were also acquired on a 3T GE Signa scanner, but the acquisition parameters for the functional images and SPGR were slightly different. The entire brain was imaged in 28 axial slices; 4.0 mm thick with a 1 mm skip between slices. Each slice was acquired parallel to the AC-PC line using a T2* weighted gradient spiral-in and spiral-out pulse sequence [TR = 2000 ms, TE = 30 ms, FA = 90° and 1 interleave, FOV = 200 x 200mm² and the effective in-plane spatial resolution was 3.125 mm (41, 42)]. To aid in localisation of functional data, a 124 slices high resolution T1 weighted 3D SPGR MRI sequence was acquired in coronal plane [TR = 35 ms, TE = 6 ms, FA = 45 , 24 cm FOV, 256 x 192 matrix].

The spiral-in and spiral-out data were combined by using a weighted average of the two images slice by slice. The weighting between the images for the spiral-in and spiral-out acquisitions was determined by the intensities of the average image so that in the regions where the spiral-out average image was of a lower intensity, the resultant image was weighted toward the spiral-in image, and vice-versa. In uniform regions the combination reverts to a simple average of the spiral-in and spiral-out images (42). Images were reconstructed, by inverse Fourier transformations, for each of the 120 time points into 64 x 64 x 28 image matrices (raw data voxel size: 3.125 x 3.125 x 5 mm). FMRI data were pre-processed using SPM99 (43). Images were corrected for movement using least square minimisation without higher-order

corrections for spin history, and normalised to stereotaxic Talairach coordinates (44). Images were then re-sampled every 2 mm (processed data voxel size: 2 x 2 x 2 mm) using sinc interpolation and smoothed with a 4 mm Gaussian kernel to decrease spatial noise.

2.6.5 Regions of Interest

Four hypotheses driven anatomical ROI, chosen *a priori*, were investigated during the categorical and dimensional studies. These anatomical ROI were anatomically circumscribed on normalised high-resolution coronal anatomical images for each of the subjects using BrainImage software (45). An expert in that area of brain anatomy, who was blind to diagnosis, drew each ROI.

2.6.5.1 Amygdala ROI

The lateral border of the amygdala ROI was circumscribed along the central, thick white matter tract in the temporal lobe until that tract was intersected either by white matter tract or by cerebrospinal fluid. The inferior border of the ROI was drawn superior to this white matter tract. The medial border was drawn along the medial aspect of the white matter tract, CSF, pons and brainstem. The superior border was drawn following the white matter tract or CSF boundary above, and the lateral border followed the thick, central white matter tract of the temporal lobe.

2.6.5.2 Fusiform ROI

The FG ROI was drawn from the deepest part of the occipitotemporal sulcus. This sulcus was followed posteriorly to the end of the cortical matter. The boundary of the cortical matter was then followed medially until the collateral sulcus, which divides the FG and the entorhinal cortex. The collateral sulcus was then followed to the deepest point where the grey matter and white matter converge.

2.6.5.3 Prefrontal ROI

The prefrontal ROI was designated using AC-PC stacks; each was orientated along the AC-PC axis on the Talairach grid and re-sliced. The AC-PC axis is identified in the mid-sagittal plane and used to define the inter-commissural line. All brain tissue anterior to the slice in which the corpus callosum first appears and bridges the left and right hemispheres, was included.

2.6.5.4 Inferior Temporal Gyrus

The ITG ROI was drawn from the point at which it was first discerned, a few slices anterior to the anterior commissure, to the brain slice on which the parieto-occipital fissure first appears. The medial border of the ITG was defined by the FG and the lateral border by the middle temporal gyrus.

2.7 Statistical Analysis

Statistical analysis of demographic, neuropsychological and ROI data in the categorical and dimensional studies was conducted using Statistical Package for Social Sciences (SPSS) version 11.5 software. Levene's test was used to ensure homogeneity of variances and Kolmogorov-Smirnov test was used to ensure that the variables were normally distributed before parametric analysis. Variables that were not normally distributed were log transformed, and if still not normally distributed, non-parametric analysis was undertaken. Standard deviations (SD) and standard errors (SE) were calculated where appropriate.

Outliers (> 3 SD) were excluded from the analysis and a two-tailed significance threshold of $p < 0.05$ applied across analyses.

2.7.1 Demographic and Neuropsychological Statistical Analysis

Ethnicity, socio-economic status, medication status, and handedness were analysed. Mean age and age range, and mean intelligence quotient (IQ) and IQ range, mean SRS score and SRS score range, mean accuracy and accuracy range and mean response time and response time range were determined for the proband and control groups. Pearson's correlation co-efficient (r) analysis was undertaken to determine the relationship between age, intelligence and SRS scores and accuracy and response time in the respective paradigms. Pearson's correlation co-efficient (r) was also calculated to determine if there was a correlation between each ROI and age, IQ, SRS, percentage correct and response time for each paradigm.

Independent samples *t*-tests were undertaken for age, IQ (FSIQ, VIQ and PIQ), accuracy and response time in the paradigms presented in the categorical studies (between group factor: diagnosis - proband group and control group) and independent samples *t*-tests undertaken. As groups were related in the dimensional studies independent samples *t*-tests were only undertaken for age, and models that incorporated family as a fixed factor used to determine differences in IQ, SCQ score, SRS score, accuracy and response time in the paradigm presented in the dimensional study (between group factor: diagnosis - proband group and control group).

2.7.2 Whole Brain Statistical Analysis

Statistical analysis to create functional activation maps from the whole brain imaging data was conducted using Statistical Parametric Mapping 99 (SPM99). FMRI data analysis was performed using SPM99 (Figure 2-5) on individual and group data using the GLM and the theory of Gaussian random fields as implemented in the SPM99 software (46). Images were reconstructed by inverse Fourier transformation into 64 x 64 x 18 image matrices (voxel size 3.75 x 3.75 x 7 mm) and images corrected for motion, normalised and spatially smoothed (Full Width Half Maximum = 4 mm) using SPM99 software (43). Data were high pass filtered and temporally smoothed. Voxel-wise *t* -scores were normalised to *z*-scores. For each subject, increases and decreases in activation were recorded by contrasting the experimental and control conditions for the respective paradigms. For each subject, a *t*-score image was generated for each contrast of interest (i.e. emotionally neutral faces - scrambled faces) and voxel-wise *t*-scores log normalised to *z*-scores. Within group significant clusters of activation were determined using the joint expected probability of height ($z > 2.65$, $p < 0.01$) and extent ($p < 0.05$) of *z*-scores (47) yielding a cluster-wise significance level of $p < 0.05$ after correction for multiple comparisons. Between groups significant clusters of activation were determined using the joint expected probability of height ($z > 1.67$, $p < 0.05$) and extent ($p < 0.05$) of *z*-scores yielding a cluster-wise significance level of $p < 0.05$ after correction for multiple comparisons. Activation foci were superimposed on high-resolution T1-weighted images and the brain areas localised with reference to the Co-planar Stereotaxic Atlas of the Human Brain (44). The overlay of functional activation maps on the structural images was used to determine the

location of functional activation during the WBA and to determine average voxel activation in the ROI analysis in all the fMRI studies presented.

Figure 2-5 Statistical Parametric Mapping

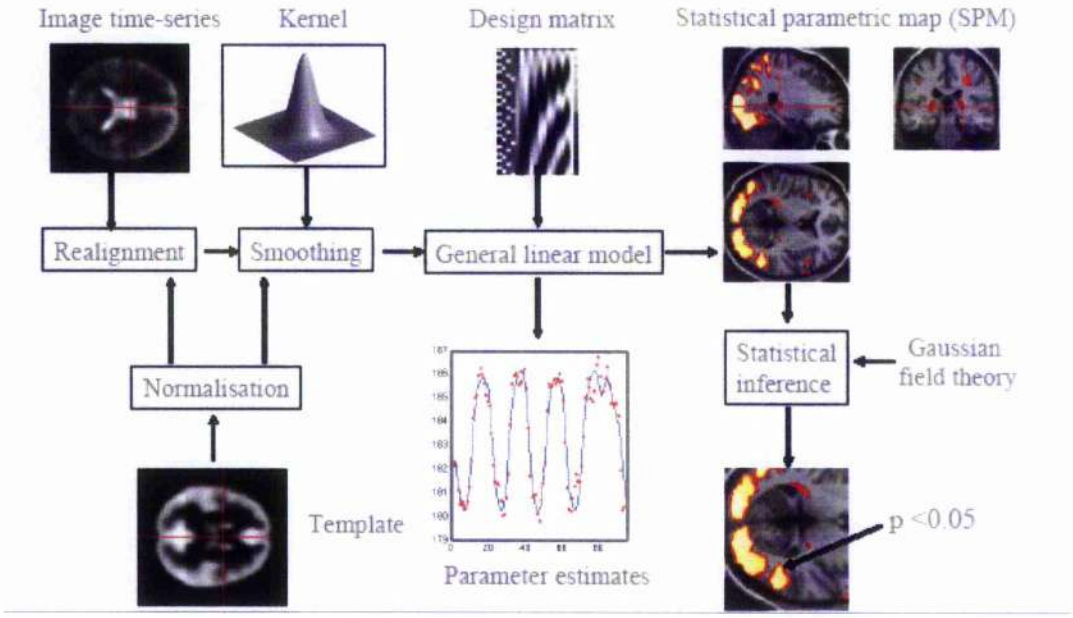


Figure 2-5 shows the imaging data processing sequence in Statistical Parametric Mapping 99.

2.7.3 Regions of Interest Statistical Analysis

All voxels containing grey matter were measured using SPM99, and the mean *z*-scores of the voxels activated above $z = 1.67$ ($p = 0.05$) were used to measure the average activation intensity within each ROI. Between group analysis of variance (ANOVA) or analysis of covariance (ANCOVA) was undertaken, if there was a significant covariant, to determine the average activation for each ROI for normally distributed data. If the ROI data were not normally distributed the groups were compared using the non-parametric Mann-Whitney U test. In both cases a two-tailed significance threshold of $p < 0.05$ was applied (between group factors: diagnosis - proband group and control group).

These methodologies were used in this thesis to address the aims of the categorical and dimensional studies. All study methodologies were approved by the Human Subjects Committee at Stanford University School of Medicine and informed consent obtained from all subjects and their parents prior to participation in the study. The limitations of the methodologies used are presented in the discussion and methodological considerations sections located at the end of each respective study chapter.

PART II: CATEGORICAL STUDIES

Chapter 3 Social Communication Impairment and Emotion Attribution from Static Facial Expressions in Individuals with Autism Spectrum Disorders

3.1 Introduction to the Categorical Studies

ASD, a categorically delineated neurodevelopmental disorder, provides an opportunity to investigate the neural correlates of emotion attribution from facial expressions in individuals with SCI who, potentially, have accrued less experience with faces and facial expressions. This chapter presents pertinent background literature on: ASD; cognitive and functional models of face and facial expression processing; and, the attribution of emotion from static facial expressions, and the aims, rationale, and hypothesis of the categorical studies.

3.2 The Autistic Spectrum

Most clinicians would agree that for 'classic' cases of autism the ICD-10, which is used in Europe (24), and the DSM-IV (25), which is used in North America, represent excellent clinical diagnostic systems. However, there are individuals who present with symptoms, which resemble those of classic autism, for whom a diagnosis of autism cannot be made. This is often because they have marked symptoms in only the first two diagnostic domains but not in the third, or because their symptoms, although as handicapping to the person, are not severe enough to meet the diagnostic criteria for autism. These individuals have been described as falling within the autistic spectrum (48), because their autistic symptoms fall along a severity continuum that includes mild to severe forms of the disorder.

3.2.1 Historical Background

Social communication is the core impairment in ASD (1) and seen in all ASD including autism, AS and PDD-NOS. SCI can manifest as inappropriate social behaviour in a wide range of reciprocal social interactions and affect the individuals' ability to fit into the social world. Presumably, throughout history, there have been people with SCI similar to what is now referred to as autism. Some of the earliest published descriptions of behaviour that resemble autism date back to the 18th century and include 'Victor, the 'Wild Boy' of Aveyron' (49). However, the word 'autism' was first introduced around 1911 by Eugene Bleuer, an Austrian psychiatrist, to refer to the progressive loss of contact with the outside world experienced by schizophrenics. In 1943, Leo Kanner, an American doctor in the Johns Hopkins Children's Psychiatric Clinic in Baltimore, described the clinical characteristics of eleven children who exhibited an 'autistic disturbance of affective contact'. He noted that these eleven children had four traits in common: a preference for aloneness; an insistence on sameness; a liking for elaborate routines; and, some abilities that seemed remarkable compared with their deficits. He considered that this phenomenon was similar in quality to the autistic child's withdrawal from the outside world, and so coined the term 'infantile autism' to describe these children who seemed to be detached from the world around them (50). Interestingly, Hans Asperger, a Austrian psychologist, unaware of the previous work by Kanner (1943), described a small group of boys between 6-11 years of age, who had marked social

interaction difficulties and motor clumsiness (51). In his original description of these children in German, he described these children as having 'autistic psychopathology'. However, it was not until 1981, when Lorna Wing, a British child psychiatrist wrote a review of this work in English (52), that the condition that has become known as Asperger Syndrome (AS) or Asperger's disorder was introduced into the English literature. As with autism, individuals with behaviour that resemble that seen in AS appear to have existed throughout history. Indeed, biblical characters such as Brother Juniper in the old testament parable of 'Brother Juniper and the Beggar' has behaviours reminiscent of individuals with AS. Throughout history individuals with these disorders, whether the disorders were recognised or not, have generated much interest.

3.2.2 Diagnostic Classification in Autism Spectrum Disorders

Since 1980 there have been many different classification systems used in North America. These classification systems include the Rutter Criteria, DSM-III, DSM-III-Revised, and now the DSM-IV. The diagnosis of autism [Online Mendelian Inheritance in Man (OMIM) 209850] emerged as a triad of impairment from expert consensus during field trials conducted to inform the production of third version of the DSM, published by the American Psychiatric Association (APA), and the 9th version of the ICD, published by the World Health Organisation (WHO).

In 1994, the APA released DSM-IV (25), which refined diagnostic criteria for autistic disorder in the North America. In the same year the WHO released a similar diagnostic manual known as ICD-10 in Europe (24). Under the auspices Professor Michael Rutter, this revision of the ICD-10 classification system had ostensibly the same diagnostic criteria as the DSM-IV classification system. This revision represented the first time that consensus had been reached in the diagnosis of autism and ensured comparability of diagnosis across Europe and North America. DSM-IV and ICD-10 classification systems are the two main clinical diagnostic systems currently in use in North America and Europe respectively.

Both DSM-IV and ICD-10 classify psychopathology based on phenomenology. This phenomenological approach recognises that it is easier to achieve consensus on phenomenological descriptions of disorder than on theoretical conceptions (53). Both classification systems define and diagnose autism by behaviour, referred to as clinical symptomatology, rather than by biological markers or aetiology. Despite much research using these categorical diagnoses no biological markers have been identified and the aetiology of autism has remained elusive. As neuroscience begins to provide the tools to inform the exploration of brain function in neurodevelopmental disorders (54) a reconceptualisation of diagnostic nosology is overdue if we are to identify the underlying aetiologies of autism (36).

3.2.3 Pervasive Developmental Disorders

Pervasive Development Disorder (PDD), is the term used in ICD-10 and DSM-IV to encompass autism, AS and PDD-NOS, but also controversially includes Rett's syndrome and Childhood Disintegrative Disorder, which are arguably aetiological distinct from the other PDD. All the disorders encompassed by PDD are described below; however, throughout this thesis the term ASD will be used to refer specifically to autism, AS and PDD-NOS, which arguably have aetiological similarities. Although PDD and ASD

appear to be used interchangeably in the literature they will be used as described above throughout this thesis.

3.2.3.1 Autism

In DSM-IV and ICD-10, autism requires the presence of symptoms in three categories of behaviour colloquially called the triad of impairment: (i.) impairment in social communication; (ii.) abnormal development of language and non-verbal communication; and, (iii.) restricted and repetitive patterns of behaviour, interests, and activities. DSM-IV criteria specify that six of the twelve symptoms listed must be present, with at least two from the social communication domain and one from each of the other two domains. Delayed or abnormal functioning in at least one of the three domains must also have been present prior to the age of three years and be sufficient to impair functioning. The criteria for autism in ICD-10 are ostensibly similar to those in DSM-IV(Appendix 1: ICD-10 Diagnostic Criteria for Autism). The symptoms listed in the DSM-IV social communication domain include: impaired use of non-verbal behaviours such as eye contact, facial expressions and gestures; failure to develop appropriate relationships with peers; and, a lack of spontaneous seeking to share enjoyment and interests. Symptoms listed in the DSM-IV communication domain include features such as a delay in or total lack of language development, pragmatic difficulties and stereotyped use of language. Symptoms listed in the DSM-IV restricted and repetitive behaviour domain include impaired pretend play and imitation and repetitive behaviours including intense preoccupations such as astrophysics, rigid adherence to routines and rituals, and stereotyped motor mannerisms such as hand flapping.

Attempts to reliably categorise autism have been compromised by the subjective nature of the level of impairment that is necessary, and sufficient, to fulfil descriptive criteria and the variable levels of expression of autistic impairment. There are many individuals who fulfil diagnostic criteria qualitatively, but do not reach the quantitative threshold for autism (55). More reliable behavioural measures of autistic symptoms have been developed to try and refine the diagnostic classification of autism (56). Instruments such as the ADI-R (20) and the ADOS-G (21) provide standardised diagnostic procedures. Such standardised approaches are crucial in cross-site studies to ensure consistent diagnosis. Researchers have argued that the criteria have been fine-tuned to the point that 'the evidence for the validity of autism is stronger than for any of the other psychiatric disorder in childhood' (48). However, despite the reliability of the ADI-R and ADOS-G diagnoses: the boundaries and validity of each of the ASD remain a matter of much debate (57); the diagnoses are still not actiologically based (58); and, neither system supports the diagnosis of AS or PDD-NOS despite their inclusion in DSM-IV and ICD-10 classification systems.

Diagnostic classification systems are in widespread use, based on the notion that reliable diagnoses are necessary for successful research into the aetiology of autism; however, some researchers believe that these classification systems group heterogeneous conditions and actually hinder biological research into psychiatric phenotypes (55, 59). The advent of technologies such as fMRI are poised to inform our theoretical conceptions of these disorders, and facilitate research to determine underlying aetiologies (36). However, it remains unclear which aspects of the autistic phenotype are the most biologically relevant for future aetiological study.

3.2.3.2 Asperger Syndrome

Individuals who show significant symptomatology, but do not meet the language criteria for autism, are diagnosed with AS. AS did not appear as a separate diagnosis until the production of DSM-IV and ICD-10 in 1994. Specifically, individuals with AS have SCI and repetitive behaviours or, more commonly, very focused and specific interests, but no history of language delay. The criteria for AS are the same as those for autism with three main exceptions: (i.) the communication and imagination impairment criteria for autism are not listed for AS; (ii.) individuals with AS do not have a clinically significant general delay in language; and, (iii.) individuals with AS do not have a clinically significant delay in cognitive development. Furthermore, unlike autism, AS is usually recognised after the age of 3 years and for this diagnosis if problems in communication and social interactions are recognised before that age they must not be of the type seen in autism (60). However, if pragmatic language delays were taken into consideration in the current DSM-IV and ICD-10 classification systems, most individuals who attract a diagnosis of AS would fulfil criteria for autism and this has led some to assert that autism and AS are not distinct conditions (61).

3.2.3.3 Pervasive Developmental Disorder-Not Otherwise Specified

Individuals who show significant symptomatology, but who do not meet full criteria for autism or AS, are diagnosed with PDD-NOS. PDD-NOS has been considered a related, but distinct, entity on the autistic spectrum; however, the boundary between PDD-NOS and other PDD diagnosis is a matter of debate (57). Many individuals have autistic-like features, which are not severe or wide ranging enough to merit a diagnosis of autism or AS, and when an individual meets fewer than six of the criteria needed for a diagnosis of autism or the criteria needed for AS then PDD-NOS is diagnosed.

Individuals given a PDD-NOS diagnosis may not meet the criteria for autism in several ways: (i.) they may not meet domain criteria in at least one of two domains (impairment in communication or the presence of repetitive, stereotyped behaviours); (ii.) they may have fewer than six symptoms in total; (iii.) they may have an age of onset after 36 months; (iv.) they may not meet all criteria for AS; or, (v.) any combination of these. PDD-NOS is seen as a catchall diagnosis for individuals who do not fit the criteria for one of the other PDD (62). The current criteria for the diagnosis of PDD-NOS in DSM-IV are somewhat ambiguous and there is a lack of consensus in the literature as to how individuals with PDD-NOS differ from individuals with autism or AS.

In one study, children with PDD-NOS were found to have better cognitive, communication, and social relatedness skills than children with autism (63). In a second study, four characteristics were found to differentiate children with PDD-NOS from those with autism and non-PDD disorders: children with PDD-NOS less often demonstrated restricted patterns of interest; had more varied make-believe play; made use of non-verbal behaviour; and, had a later age of onset (64). In a third study, individuals with PDD-NOS had less restricted stereotyped behaviours than individuals with high functioning autism (HFA) (65). Individuals receiving a diagnosis of PDD-NOS usually had strong evidence of impairment in reciprocal social interaction, but fewer autistic symptoms than children with autism, especially in the domain of repetitive stereotyped activities (66).

Despite the diagnostic uncertainty, PDD-NOS is the most common form of ASD as it encompasses: individuals expressing some autistic symptoms; those expressing the broader autism phenotype (BAP); and, those that also fulfil criteria for other childhood disorders such as ADHD (67). However, despite being the commonest PDD group, individuals with PDD-NOS are often excluded from research because the category lacks specific inclusion criteria. The lack of specific inclusion criteria for the individuals with PDD-NOS has led to PDD-NOS being termed a diagnosis of exclusion (66). In the initial DSM-IV autism/ other PDD field trials (68), the overall agreement between clinicians on the differentiation of autism from non-PDD conditions was 0.95, but fell to 0.65 when differentiating between autism and other PDD including PDD-NOS (69).

Ambiguous criteria mean that the boundaries of the PDD diagnostic categories are unclear. The exclusion of individuals with PDD-NOS reduces the power of genetic studies to determine susceptibility genes for the SCI seen in ASD, by excluding individuals who have a SCI with a similar underlying aetiological to autism and AS. The continued exclusion of this, the commonest group of individuals with SCI, is not only unethical, but contributes to the fractionation of individuals with qualitatively similar SCI into multiple diagnostic groups, reducing the power of aetiological studies to detect the aetiology of the SCI seen in ASD.

3.2.3.4 Rett's Syndrome and Childhood Disintegrative Disorder

Two additional disorders are controversially included in the PDD diagnostic category: Rett's Syndrome and Childhood Disintegrative Disorder. Although these disorders have become regarded as aetiologically distinct, there has been a recent revival of interest in possible commonalities with ASD.

Rett's Syndrome

Rett's Syndrome, first described by Andreas Rett in Austria in 1966 (70), is an X linked neurological disorder, which affects only females, in which there is a distinctive pattern of developmental regression resulting in neuromotor and neurocognitive deficits. Characteristically there is a period of normal development and then, between the age of 1 to 4 years and then the onset of symptoms. The first symptom is usually the loss of muscle tone with progressive loss of previously acquired skills such as the loss of purposeful hand skills and replacement with repetitive hand movements such as wringing, washing, licking, or clapping (71). Other features include diminished ability to express feelings; avoidance of eye contact, a lag in brain and head growth, gait abnormalities and seizures. There is also severe impairment in expressive and receptive language development (25). The syndrome affects approximately 1 in every 10,000-23,000 live female births (71). Recent reports suggest that up to 75% of cases Rett's syndrome is due to a genetic mutation on the X chromosome at the gene MECP2 (72). From this brief description it is possible understand why some do not regard Rett's syndrome as an appropriate inclusion in the PDD category. However, some individuals with Rett's syndrome have marked autistic symptoms, and since the discovery of the genetic mutation for Rett's syndrome on the X chromosome (Xq28), there has been revived interest in the possibility of genetic overlap with autism. Revived interest centres on the identification of genetic overlap as this would map those autistic symptoms expressed in Rett's syndrome to a gene on the X chromosome in the Rett's locus.

Childhood Disintegrative Disorder

Childhood disintegrative disorder is an uncommon condition characterised by marked regression in multiple areas of functioning following at least two years, and in most cases 3-4 years, of apparently normal development in the absence of an associated medical condition and is associated with severe cognitive impairment (73). Loss of skills occurs in at least two of the following areas: expressive or receptive language; social skills or adaptive behaviour; bowel or bladder control; play; or, motor skills. Behavioural features of autistic disorder must be present in at least two of the following areas: qualitative impairment in social interaction; qualitative impairment in communication and play; and, restricted repetitive and stereotyped patterns of behaviour (25, 62). Two studies suggest that the prevalence ranges from 0.2 to 1.7 per 10,000 individuals (74, 75). There has been recent interest in determining whether childhood disintegrative disorder is distinct from autistic regression, which occurs in the first two years of life (76), or if both represent a genetic subtype of regressive autism with a distinct aetiology (77). At present, the underlying aetiology of childhood disintegrative disorder is unknown; however, potentially studies of this subtype of regressive autism could inform future aetiological studies of ASD.

3.2.4 Autism Spectrum Disorders

As previously, discussed PDD refers to the DSM-IV/ ICD-10 category, which includes autism, AS, PDD-NOS, Rett's disorder, and Childhood Disintegrative disorder. The term 'autism spectrum disorders' was introduced to incorporate impairment upon the autistic continuum, which does not fulfil diagnostic criteria for autism (78), and includes autism, AS and PDD-NOS.

3.2.4.1 Prevalence of Autism Spectrum Disorders

A recent review of epidemiological studies found the median prevalence rate for autism in 16 surveys published between 1966 and 1991 to be 4.4/ 10,000, compared to a median rate for 16 surveys published in the period 1992-2001 of 12.7/ 10,000, suggesting an increase in prevalence estimates for autism in the last 15 years (79). Conservative prevalence estimates for autism currently stand at 10/ 10,000, with estimates for AS at 2.5/ 10,000 and PDD-NOS at 15/ 10,000, making a combined prevalence for all ASD of 27.5/ 10,000 (80). However, three of the most recent studies provide estimates that are approximately twice as high as the above figure for all ASD, with the true prevalence of ASD likely to be within the range of 30-60/ 10, 000 cases (81-83). Although this represents a huge increase from the original estimate 40 years ago, which reported 4.1/ 10,000 population (84) existing epidemiological data are inadequate to properly test hypothesis on changes in the incidence of autism and upward trends in rates of prevalence of autism cannot be directly attributed to an increase in the incidence of the disorder (80).

While this apparent increase in prevalence has led some to propose various environmental actiologies for autism. Other possible explanations for the apparent increase include: (i.) better recognition and diagnosis of the disorder; (ii.) diagnosis of autism instead of mental retardation; (iii.) increased recognition of the existence of a spectrum of autistic disorder; (iv.) awareness that the manifestations of the core triad of impairments may vary considerably especially in higher functioning individuals; (v.) better ascertainment of milder cases in epidemiological studies; and, (vi.) an actual increase in the frequency of disorder (85-87). The increase is likely to be largely a consequence of improved

ascertainment and a considerable broadening of the diagnostic concept; however, a true increase in risk due to some, as yet to be identified, environmental risk factor has not been ruled out (88).

Recent epidemiological studies have shown that PDD-NOS is at least twice as common as autism in the general community, and that ASD other than autism, show the greatest rate of increase in the general population (80, 83). These studies estimate that around 70% of individuals with autism are mentally retarded, that is have an IQ below 70. However, when individuals with more broadly defined ASD are included, the proportion of affected individuals with co-morbid mental retardation decreases substantially and less than half of children with ASD were found to have performance IQs of less than 70 (83). Indeed, when ASD is more broadly defined a recent study suggests that the prevalence of autistic traits is substantially greater than previous recognised. This study reported the prevalence of autistic traits as 1% in a population cohort of children in the South Thames area of the United Kingdom (89).

3.2.4.2 Identification of Autism Spectrum Disorders

While autism can be identified as young as 18 months, it is more commonly and reliably, diagnosed at around the age of three years or older (90). The mean age of diagnosis in autism is 5 ½ years, although with hindsight parents have often been aware of developmental difficulties from 18 months of age in autism. However, individuals with HFA and AS are often not diagnosed until late in childhood, and the mean age of diagnosis reported for AS is 11 years (91).

3.2.4.3 Intelligence and Autism Spectrum Disorders

Historically autism has been associated with learning disability; however, there are many individuals, who are high functioning in terms of their general intelligence and language abilities, for whom social communication is still a major difficulty. In these cases, it is important to emphasise that it is the individual that is high functioning, not the autism, which remains marked. High functioning individuals with ASD, who have repetitive/ stereotypical behaviours or interests and language delay prior to the age of three years, attract the diagnosis of HFA. This term was introduced by DeMyer in 1981 (92), and although, there are no explicit guidelines for the diagnosis of HFA, the current convention is to diagnose HFA when the individual's intelligence is above 70 (93). High functioning individuals with ASD, repetitive/ stereotypical behaviours or interests without language delay, have attracted the diagnosis of AS. These criteria are in keeping with those of Hans Asperger, who believed that social communication, and not intellectual or language delay, was the main impairment in AS (51). The validity of the diagnostic boundary between HFA and AS, which is based on language delay before the age of three years, continues to be a matter of debate in both research and clinical circles (94). Evidence of delayed or abnormal language development prior to the age of three years actually pertains to semantic language development and the relevance of semantic language in determining HFA and AS categories is unresolved. Both individuals with AS and HFA actually have pragmatic language deficits as part of their SCI. Some researchers have concluded that language delay is not a suitable differentiating variable for categorisation into PDD sub-groups (61). Characteristics of AS are often associated with HFA, indeed individuals have been reported to fulfil mixed criteria (95, 96), and AS and HFA often difficult to differentiate (97). Individuals with autism and AS may co-exist within the same family, which further suggests that these disorders represent differences in severity of disturbance rather than different entities

(98). High functioning individuals with SCI are also diagnosed as having PDD-NOS. High functioning individuals given a PDD-NOS diagnosis have an IQ above 70 but only meet criteria for autism in the social impairment domain of the DSM-IV. They do not fulfil full criteria for autism because they: do not meet criteria in at least one of the other two diagnostic domains (language impairment or the presence of repetitive, stereotyped behaviours); have fewer than six DSM-IV criteria symptoms; have an age of onset after 36 months or any combination of these and also do not meet all DSM-IV criteria for AS. The nosological validity of AS, HFA and other high functioning PDD subtypes as discrete entities will only be validated if differences in outcome, aetiology, or treatment are found. However, at present there is little to evidence to validate such a notion (58).

3.2.4.4 Socio-demographic Factors and Autism Spectrum Disorders

Kanner's initial report stated that children with autism were disproportionately likely to have parents from high socio-economic backgrounds (50). However, although high socio-economic status has been associated with higher rates of autism in some small samples review of larger, well-designed studies does not support any association between socio-economic status or immigrant status and autism (80). A recent epidemiological study of children born in California between 1989-1994 reported an increased risk of autism for males, multiple births and children born to black mothers (99).

3.2.4.5 Gender and Autism Spectrum Disorders

Across studies, autism is more common in boys than in girls, with a mean sex ratio of 4.3:1 across epidemiological studies. The male preponderance appears to be higher in individuals of normal intelligence with a median male: female ratio of 5.75:1 reported when 12 studies of non-retarded individuals with autism were reviewed, and a median sex ratio of 1.9:1 reported when 11 studies of moderate to severely mental retardation individuals with autism were reviewed (80).

3.2.5 Co-morbidity of Autism Spectrum Disorders

3.2.5.1 Co-morbid Neurodevelopmental Disorders

In addition to the diagnostic issues described, qualitatively similar SCI is also seen in high functioning individuals with SCI, who attract neurodevelopmental diagnoses such as non-verbal learning difficulties (NLD) (100), semantic pragmatic disorder (101), sensory integration dysfunction (102) and social-emotional processing disorder sometimes referred to as right hemisphere disorder (103). Individuals with SCI often have other co-occurring neurodevelopmental disorders such as ADHD (67), Tourette's syndrome (104) and tic disorder (105).

3.2.5.2 Co-morbid Psychiatric Disorders.

The relationship between autism and psychiatric disorders such as schizophrenia is controversial with some studies suggesting that the current diagnostic criteria have to be revised to acknowledge the co-morbidity in ASD, and other studies finding similar co-occurrence to the general population (106, 107). Individuals are reported to often have other co-occurring psychiatric disorders such as obsessive compulsive disorder (108), anorexia nervosa (109) and depression (110). Social understanding deficits have also been shown to exist in conduct disorder populations at a higher than expected rate suggesting

that the social and communication deficits particularly in individuals with onset of conduct disorders at a young age may be mediated by autistic spectrum symptomatology (111).

3.2.6 Environmental Factors and Autism Spectrum Disorders

Environmental factors such as measles, mumps and rubella (MMR) triple vaccine have been proposed as causal in autism (112), and then retracted (113). Currently toxins such as thimerosal are hotly debated as potential causal factors in the aetiology of autism (114-116). However, epidemiological studies to date do not supported a causal relationship between environmental factors such as MMR (117, 118) or thimerosal (119) and autism. Although there is an increased prevalence of obstetric complications among autism cases this is most likely due to the underlying genetic factors or an interaction of genetic factors with the environment (120). Birth order, especially first and last or later born, and older maternal age have been associated with an increased risk for autism (121).

Other psychologically mediated risk factors have also been suggested. Leo Kanner introduced the concept of autism as a maternally mediated psychological disorder of emotional detachment and introduced the term 'refrigerator mother'. This resulted in generations of mothers of autistic children being accused of causing their child's disorder. Today autism is widely recognised to be a one of most genetic of all psychiatric disorders (88), and no longer considered a psychologically mediated disorder.

3.2.7 Genetic Studies of Autism Spectrum Disorders

Numerous twin and family studies support a genetic predisposition toward autism. Although only a minority of cases of autism (10-25%) are associated with recognised medical disorders of known aetiology (122-124), this association with numerous medical disorders of different aetiology suggests the presence of multiple underlying aetiologies for autism - a phenomenon known as heterogeneity.

Aetiological heterogeneity (the same disorder arising from several independent aetiological causes), which includes genetic heterogeneity (the same disorder arising from different independent genetic causes), and behavioural heterogeneity (different disorders arising from the same underlying cause), are both evident in the small proportion of autism cases that are associated with known genetic conditions [e.g. fragile X (125), tuberous sclerosis (126) and phenylketonuria (127)]. The heterogeneity seen in autism associated with numerous medical disorders suggests that idiopathic autism, a term used when there is no identified cause, is also likely to be a heterogeneous condition (128).

3.2.7.1 Twins

There is strong evidence from twin studies to support the importance of genetic factors in the development of idiopathic autism. Several epidemiological same-sex twin studies have demonstrated significant differences in the monozygotic (MZ) and dizygotic (DZ) twin concordance rates (129-131). The largest of these studies found that 60% of MZ pairs were concordant for autism compared with 0% of the DZ pairs, suggesting a heritability of > 90% assuming a multi-factorial threshold model (129). However, recent studies have suggested a reduced twin concordance for autism in MZ twins (132), and have proposed that twin studies need to be replicated using the current diagnostic criteria. The marked difference in pair-wise concordance between MZ and DZ twins, and the rapid fall off in the rate of autism

with decreasing genetic relatedness, point to the involvement of multiple genetic loci, probably acting epistatically (genes acting on genes). Some authors propose the involvement of three or four loci (133), with others proposing that the number of loci may be greater than fifteen (134).

The findings from several twin studies have suggested that the autism phenotype extends beyond diagnostic boundaries (129, 130). One twin study, in which one or both of the twins were autistic, found that most of the non-autistic MZ co-twins exhibited milder social and communicative abnormalities related to autism (135). However, despite evidence for genetic transmission in autism, progress in identifying the underlying aetiology involved in autism has been hampered by both phenotypic and genetic heterogeneity. Variable expressivity, where the same causal factors lead to a range of phenotypes, and variable penetrance, where the expression of the genetic liability leads to a range of phenotypes, is supported by family and twin studies (136) and has also hampered aetiological studies.

3.2.7.2 Singletons

The rate of autism in singleton siblings is the same as for DZ twins and in the range of 2-6% (128). Accounting for stoppage (the increased tendency for parents of autistic children to have fewer children following their first autistic child) the sibling recurrence risk for autism is around 8.6% (137). Assuming the prevalence rate of autism in the general population is between 5 and 17 per 10,000, the sibling relative risk ranges from 50 to 175 (83, 138). This makes the familiality of autism very many times higher than many other psychiatric and neurodevelopmental disorders, such as schizophrenia (139) and ADHD (140), which also have strong, but complex, non-mendelian genetic determinants.

Although, there is strong evidence that autism is a strongly genetic condition, controversy exists with regard to the genetic aetiology of AS and PDD-NOS. Large genetic studies of autism such as the study undertaken by the International Molecular Genetic Study of Autism Consortium (141) have identified genetic loci associated with autism, and even larger collaborative studies such as the Autism Genetics Project are poised to further inform autism genetic research (142). However, identification of genetic loci and utilisation of what has been termed a 'bottom up' approach (e.g. identification of genetic loci and fine mapping of the loci to identify genes that may be relevant for the autistic phenotype) has not been particularly successful approach to identify genes and gene function in ASD. Many groups are focussing on improved delineation of the autism phenotype to facilitate the identification of genes and gene function and using approaches such as sub-typing and quantification of phenotypic information that may be more closely related to the genetic aetiology. The identification, in what has been termed a 'top down' approach, of aetiologically valid models based on constructs that are more closely related to the genetic aetiology would facilitate the aetiological study of ASD. In these models, findings from behavioural, cognitive and functional levels of explanation would constrain and inform each other (4, 5) to reduce the heterogeneous nature of the autistic phenotype (11). Previous explanatory models have proposed different primary cognitive deficits in ASD. These cognitive models and the degree to which they have been shown to be more aetiological relevant is reviewed in the following sub-sections.

3.2.8 Cognitive Models of Autism Spectrum Disorders

Attempts to construct explanatory cognitive models have mainly centred on autism. These explanatory cognitive models have focused on primary cognitive deficits in an attempt to explain autism as a unitary syndrome and multiple primary cognitive deficits to explain one or more dimensions of behaviour in autism. A single primary cognitive deficit (143) would be an attractive way of explaining the regular co-occurrence of triad of symptoms characteristic of autism, and would justify the use of a an 'umbrella' term such as autism for this constellation of symptoms. The criteria for a primary cognitive deficit have been defined as universal, unique, necessary and sufficient to explain the symptoms of the disorder, in other words, the cognitive cause of the behavioural symptoms seen in the disorder (144). Universality, uniqueness, and explanatory value (145, 146), and an additional criterion - causal precedence (147) have been the key criteria used to judge the primary nature of proposed cognitive deficits in autism. Other criteria frequently cited as signifying a primary cognitive deficit include the existence of the cognitive deficit or BAP in relatives of individuals with autism and the over-representation of the cognitive deficit in the families of individuals with autism (4, 5).

The notion of a single primary cognitive deficit underlying autism as a unitary syndrome has been challenged by those that advocate that multiple primary deficits are necessary to explain the whole syndrome, and by those that argued against autism as a unitary syndrome that requires a single unifying level of explanation (148). The latter argue that either autism should be divided into multiple distinct sub-groups, or multiple dimensions based on shared common aetiology. There would, therefore, be more than one cognitive deficit, each underlying a different sub-group or dimension such as symptom domain, number of symptoms, severity of symptoms or level of functioning (149). The notion of autism as a uni-dimensional syndrome is compatible with autism as a unitary syndrome, and would facilitate the investigation of the cognitive and functional correlates of autism. This notion of autism as a uni-dimensional syndrome is reviewed in Part III, Chapter 7 of this thesis.

The three main single primary cognitive deficits that have been previously advocated as an explanation of autism as a unitary syndrome are theory of mind (TOM), executive function (EF) and weak central coherence (CC). These primary cognitive deficits are reviewed in the following sub-sections. Review of these explanatory cognitive models focus on the criteria for a primary cognitive deficit (144), but as more recent attempts to construct explanatory cognitive models have centred around cognitive construct(s) that offer potential biological explanation, research on the biological correlates of each construct is also reviewed.

3.2.8.1 Theory of Mind

TOM is the one of the most influential constructs currently used to refine the characterisation of the social phenotype in autism (150). This model of social development proposes that being able to conceive of mental phenomena, such as mental states in others, is the foundation mechanism that makes 'inter-subjectivity' possible (151). Inter-subjectivity between mother and infant implies relatedness at a pre-verbal stage of development and entails sharing joint attention, sharing intentions and sharing affective states (152).

In the past few years, a number of limitations to the explanatory power of the TOM have been raised. Studies have shown that individuals with bilateral amygdalectomies (153) and deaf children (154) have comparable rates of failure on TOM tests, demonstrating that TOM deficits occur in a number of other disorders, and are not specific to autism. Many autistic children do not show normal social skills in infancy and early childhood (155), and home video studies of toddlers later diagnosed as autistic have revealed social withdrawal, motor stereotypy and lack of attachment prior to age 3 (156, 157). This is the age at which TOM develops, suggesting that SCI predates impaired TOM in autism, and providing evidence against the primacy of TOM. The greatest limitation to the explanatory power of the TOM, however, has emerged from studies of cognitively able individuals with autism. Despite their pronounced social disability 15-60% of autistic individuals pass current TOM tests (158). This means that the TOM tasks currently in use, either lack specificity or sensitivity to detect TOM impairment or suggest that TOM is not the primary cognitive deficit in ASD. High functioning individuals with ASD have been shown to be capable of conversing with others about mental states in some situations (159, 160). However, these skills do not translate into social competence in naturalistic environments (161), and successful attempts to teach TOM skills in a therapeutic programs have not translated into improved social or communicative competence (162).

The relative success of cognitively able individuals with autism in the performance of TOM tasks may result from a series of factors that foster or 'scaffold' task performance on experimental tasks, but do not facilitate social adaptation in real life (163). High functioning individuals with ASD have been reported to perform better on verbally mediated tasks (164) and may employ a verbally mediated strategy to successfully complete the task, whereas, communication demands in real-life social situations often depend upon non-verbal social cues. To reduce verbal mediation, AS and HFA individuals have been studied in tasks such as the Social Attribution Task (SAT). The SAT involves the attribution of social meaning to 'geometric' figures in a short cartoon movie. High functioning individuals with ASD used pertinent TOM terms very infrequently during the SAT, and did not derive psychologically based personality features from the shapes movements, even when provided with more explicit verbal information on the nature of the cartoon (163). This study further highlighted the social understanding deficits in ASD when tasks require the attribution of intent and emotion to derive social meaning.

Until recently, TOM tasks were not sensitive to social impairment in individuals beyond the developmental age of 11 years. Recently, in an attempt to biologically validate TOM tasks, several advanced TOM tasks have been developed to capture the more subtle TOM deficits in less disabled older autistic populations (165, 166). One such task called the 'eyes' task (167) has allowed the measurement of TOM into adulthood in otherwise cognitively high functioning individuals. However, the eyes task is not a TOM task in the traditional sense and could better be described as an emotion attribution task from the eyes region of the face. Interestingly, the eyes task has also been studied in siblings of high functioning young men with ASD and emotional attribution deficits found when compared to the siblings of typically developing controls suggesting that reduced expertise in the attribution of emotion from the eyes region of the face may be familial (168). When the eyes task was undertaken in the scanner the amygdala and areas of the prefrontal cortex showed increased activation in typically developing

individuals; in comparison, individuals with autism or AS only activated the fronto-temporal regions when attributing emotions from the eyes (167). Therefore, there is preliminary evidence in small samples to suggest that emotion attribution from the eyes region may represent an aetiologically relevant 'TOM' task in individuals with ASD. Although genetic studies of emotion attribution and other TOM abilities are still lacking, an emerging neurofunctional literature has already delineated viable brain models of mentalising capacities in TOM tasks. FMRI studies of the 'Strange Stories' and 'Sally Ann' type mentalising tasks have been undertaken with individuals. These studies support that left medial prefrontal cortex is a crucial component of the brain system that underlies the normal understanding of other minds and that individuals with ASD do not activate this region during TOM tasks (169).

In summary, the relationship between the behavioural, cognitive and functional levels of research have not been thoroughly investigated in TOM research, and integration between these different levels of interrogation is still lacking. The explanatory power of TOM is ultimately reduced by the failure to demonstrate direct correlation between social impairment and TOM skills (170). Although TOM measures remain one of the central candidates for better characterisation of the social phenotype in autism, the validity of the traditional TOM construct in autism is still in question.

3.2.8.2 Executive Function

EF refers to a group of neuropsychological skills that allow a person to maintain an appropriate problem-solving set in order to attain a goal. There is substantial evidence to support EF deficits in high functioning autistic individuals (146, 171). Among the various constructs subsumed under EF, planning and 'set-shifting' are the skills most affected in autism. EF has face validity given that individuals with autism are known to perseverate on inappropriate responses and to have great difficulty planning and organizing their daily activities. Again, deficits in EF are not unique to autism and are seen in a number of other disorders. Studies have shown differential aggregation of deficits in EF in parents (172) and in siblings of autistic probands (173) suggesting that this construct may be familial. Recent fMRI studies have explored the neural correlates of EF in ASD (174). However, EF does not account for the other cognitive deficits seen in autism, and would appear to be insufficient to explain the social impairment seen in individuals with autism (175).

3.2.8.3 Central Coherence

Both TOM and EF struggle to explain aspects of autistic behaviour. An alternative account of the primary cognitive impairment suggests that autism is characterised by a cognitive style biased towards local (otherwise known as component or feature-based) information processing, rather than global (otherwise known as configural or holistic) information processing – this style is termed weak CC (176). CC was first proposed as the primary cognitive deficit in autism by Frith in 1989. Frith's model made no distinction between social and non-social information processing, but argued that weak CC results in the individual failing to understand the context in which social interaction occurs. CC has the capacity to explain the relative strengths in visual processing seen in autism in visual search (177) and visio-spatial tasks such as block design tasks (178). Individuals with autism have been reported to have weak CC, which is the reduced tendency to integrate local information in the search for global meaning, and are reported to focus on the parts of any stimulus rather than the whole. Studies have linked poor TOM to

weak CC (179), and there is evidence that weak CC might explain aspects of the extended autism phenotype as well as characteristics seen in some of the relatives of people with autism (180, 181).

Although, the model proposed by Frith was psychological, neurofunctional evidence in support of the model is emerging. Visual processing studies of individuals with autism support a predisposition to local rather than global modes of information processing in autism (17). Studies have also shown that during visual search tasks individuals with autism invoke a strategy more dependent on visual systems such as the ventral occipito-temporal regions for feature analysis (182). This perceptual processing bias may lead to some of the social processing difficulties seen in autism.

CC is appealing as an explanatory construct for autism because it captures the characteristic processing style seen in autism, which is marked by attention to fragmented and isolated aspects of the environment, and to the neglect of context and global meaning. This characteristic processing style potentially explains the aptitudes, as well as the deficits, seen in individuals with autism and has the capacity to explain some of the abnormalities seen in face processing in some individuals with autism. The explanatory significance of reduced activation in the brain areas associated with configural and feature-based processing for the attribution of emotion from facial expressions and SCI seen in ASD has not been explored, and will be the focus of investigation in this thesis.

The extensive literature pertaining to the cognitive deficits in ASD is reflected in the lengthy nature of the above section. TOM and EF do not fulfil criteria for a primary cognitive deficit and do not explain the aptitudes seen in ASD. CC potentially explains the aptitudes, as well as the deficits seen in individuals with autism and fulfils some of the criteria for a primary cognitive deficit in ASD. Therefore, this visual processing style is of interest when considering explanations for the SCI seen in individuals with ASD. Face and facial expressions processing in ASD are reviewed in the next sub-sections.

3.3 Face and Facial Expression Processing

Over the past two decades, research in autism has shifted focus from cognitive models, such as those discussed in the previous section, to models of social dysfunction based on normative socialisation processes in typically developing individuals. Seminal studies in the late 1990's shifted the focus of early detection of autism to social orientating behaviours (183, 184) and more recently, a great deal of attention has concentrated on studies of face processing. In particular attention has focused on facial identity recognition (185, 186) given the central role of face perception in the process of social communication and there are strong models of face processing skills in typically developing (187) and autistic populations (18, 188).

Newborn infants, less than two days old, show a preference for face-like patterns (189) and typically developing infants seem to have an innate preference for looking at faces (190) rather than other objects, providing evidence that these social orientating behaviours are present from a very young age. Preferential viewing patterns including attention to eyes rather than mouths, and attention to social rather than inanimate objects are established in the first year of life (191). Orienting to face-like stimuli and face-tracking behaviour can be observed within the first few days of life (189, 192).

Behavioural studies show that newborns can discriminate between individual faces (193) and emotional expressions (194). Early studies found that children between the ages of 8 and 10 years switch from a reliance on 'piecemeal' processing to 'configural' processing of unfamiliar faces (195). Subsequently researchers found evidence of configural or holistic processing of faces in children as young as 6 years of age (196). More recent studies have demonstrated that although very young children first develop acumen for feature-based processing of the eyes, they also have rudimentary configural processing capacity for the face, which continues to mature into adulthood (197).

In autism, home videos in the first year show impairments in reciprocal social interaction including lack of social smile, lack of appropriate facial expression and poor social attention to faces (157, 198). These studies suggest that social orientating behaviours, particularly joint attention behaviours, are the best discriminators of autism in children as young as 20 months of age (199), and related to the outcome in autism (200). The lack of interest in the faces of others in the first six months is one the best predictors of a later diagnosis of autism (201). Studies also show that children with autism are not as socially motivate, and spend less time viewing faces (199). Individuals with ASD fail to develop the skills to understand subtle facial expressions, which are thought to require experience and hence necessitate both exposure and interest (202). Children with autism have also been reported to avert their gaze from direct eye gaze (203) and not use eye-gaze for social and communicative purposes (204). Indeed individuals with autism are widely reported to use atypical face processing strategies (205). Studies that have focused on patterns of attention and face processing, such as a recent eye-tracking study, have found that in individuals with autism there was a strong positive correlation between the viewing time focused on mouths (but not on eyes) and social competence. This raises the possibility that, by focusing on mouths, individuals with autism attain some understanding of social situation, perhaps via focusing on speech. There was also a strong negative correlation between time viewing objects and social competence, which raises the possibility that by focusing on objects individuals with autism are neglecting to focus on stimuli of social significance (205). In real-life social situations, many crucial social cues occur very rapidly and relate to facial expressions, and failure to notice these social cues may lead to a general failure to assess the meaning of entire social situations.

In contrast to the three main single primary cognitive deficits (TOM, EF and CC) that have been previously reviewed as potential explanations of autism - atypical face and / or atypical facial expression processing would offer a more obvious explanation for the SCI in ASD. Both cognitive and functional levels of explanation of face and facial expression processing in ASD and typically developing individuals are reviewed in the following sub-sections; however, deficits in facial expression processing, as opposed to face processing, may be of most relevance when considering the SCI in ASD (1).

3.3.1 Cognitive Models of Face Processing

Faces are complex three-dimensional surfaces that are processed using component or configural processing in typically developing individuals. Feature or component processing (also termed componential, piecemeal, and local processing) has been used to refer to visual processing of separable local elements within the face, which are perceived as distinct parts such as the eyes, nose, mouth and chin. Holistic or configural processing (also termed global processing) has been used to refer to the

processing of the face as a whole or 'gestalt' (206). The featural/ holistic, component/ configural and enhanced local perceptual precedence models of face processing are all based on these forms of processing but place different emphasis on these forms of face processing, and relate to CC theory in a different fashion. The literature on the featural/ holistic, component/ configural and enhanced local perceptual precedence cognitive models of face processing is reviewed for typically developing individuals and individuals with ASD in the following sub-sections.

3.3.1.1 Featural/ Holistic Model

In 1993, Tanaka and Farah proposed a holistic model for face recognition in typically developing individuals, in which information about the features of the face and their configuration are combined together in the face representation. The implication of this hypothesis is that alterations in facial configuration interfere with the retrieval of facial features, hence, emphasising the interdependency of featural and configural processing in a holistic face representation (207). According to the holistic face processing hypotheses upright faces are stored as unparsed perceptual holes in which individual (component) parts are not explicitly represented (208). Evidence against purely holistic face processing has accrued, which suggests that face components and configural information are both encoded, and stored explicitly when typically developing individuals process upright faces (207).

Although, in ASD research the term 'holistic processing' has been used interchangeably with configural processing strictly speaking holistic face processing assumes that adults process the whole face as unparsed percepts. In one recent study, autistic children were reported to use holistic face processing, but this was mainly evident when face recognition was dependant on the viewing of the mouth region of the face, and the reverse of that seen in non-autistic individuals (206). In contrast to their proficiency in processing mouth cues, children with autism were markedly deficient when face identification depend on the eyes; therefore, holistic processing impairment did not fully explain the processing abnormalities in autistic face recognition seen in this study (186).

3.3.1.2 Component/ Configural Model

The development of configural processing has been related to the specialisation of visual areas involved for face processing (209). The configural processing model presupposes that when the significance of the stimulus is determined by the combination of two or more features, those features are unified in to a single representation as a configuration, and that this configural representation is qualitatively different from the separate representations of each individual feature (210). Configural face processing proposes that the ability to configurally process faces improves over many years at the expense of flexibility with other visual percepts. A recent study showed that configural processing develops later than feature-based or component processing, and suggested that configural processing skills may continue to develop in adolescence (211).

According to the component/ configural hypothesis, the processing of configural information is much more impaired by changes in orientation than the processing of component information. This differential increment, which was first described by Sergent and colleagues, has been termed the face inversion effect

(206) and the lack of this effect in different study populations has been widely used to infer configural face processing deficits.

In autism, seminal studies found reduced face inversion effects in the performance of children with autism (212, 213). Autistic children have been found to be better at recognizing isolated facial features, and partially obscured faces, than typical children (212, 214). Individuals with autism also recognise inverted faces better than control participants (212, 213) and spend equal time looking at inverted faces and non-inverted faces compared to controls (215). It has been proposed that this pattern is secondary to a failure to process faces configurally (216), and that it provides evidence of an emphasis on local detail in ASD rather than global whole as seen in typically developing individuals (217).

3.3.1.3 Enhanced Local Perceptual Precedence Model

Enhanced local perceptual precedence has been proposed as an alternative explanation to configural processing deficits for the predisposition toward local processing in autism. According to predictions from the weak CC theory for perceptual processing, persons with autism should display a tendency to focus on details rather than on the bigger picture (218) and display configural processing deficits. However, the evidence for CC theory is not consistent with enhanced detection of local targets and typical global processing has been reported in some studies of individuals with autism (219, 220). Indeed, there are studies that suggest that individuals with autism have the capacity to globally process stimuli in the same way as typically developing individuals or are at least able to process globally when primed to do so. However, when not primed to process globally, individuals with ASD exhibit a preference toward the local or feature-based processing of information (221-223). From these studies, abnormalities in perceptual processing that serve to enhance the salience of individual stimulus features, but do not compromise processing of global configurations (224), have been proposed as the predominant processing style in autism. This has been encapsulated in the enhanced local precedence perceptual hypothesis, which predicts that the features are more salient and acutely represented. The enhanced local perceptual precedence hypothesis (225) predicts that autistic individuals would not have a deficit in configural processing but, rather than focussing on the configuration of the percept, would focus on the features as they were of more salience. Studies of autism and adolescents with HFA have found locally oriented perception and intact global processing among individuals with ASD (221-223).

These cognitive models do not directly address the paucity of an aetiological explanation for SCI, but do inform the development of cognitive paradigms to explore the neural correlates of face processing in fMRI experiments. Brain regions involved in face processing in typically developing individuals and individuals with ASD are reviewed in the next sub-section.

3.3.2 Functional Models of Face Processing

Imaging experiments have shown that young infants' brains initially process upright human faces, inverted human faces, monkey faces and objects all in a relatively similar way, activating the same brain areas across both hemispheres (193, 226). With brain development, brain processing of human upright faces becomes increasingly specialised and localised to the right FG (227). The lateral aspect of the middle part of the right FG has become known as the fusiform 'face' area (FFA) (228) and has strongest

activation to faces (229). There is longstanding debate whether expertise for face processing is as a result of innate or experience-dependant specialisation of the right FG for face percepts (228, 230, 231). The innate and experience-dependant specialisation fusiform models have been increasingly interrogated with the advent of fMRI and are reviewed in the following sub-sections. These two functional models have been predominantly developed through studies of face recognition in typically developing individuals. The explanatory consequences of these two functional models are discussed in terms of face processing in typically developing individuals and the functional brain abnormalities seen in face processing experiments in individuals with ASD.

3.3.2.1 The Innate Fusiform Specialisation Model

In typically developing individuals, Kanwisher and colleagues have argued that the right FFA is an innate modular region specialised specifically for face processing. They found that this area was significantly more active in typically developing individuals when viewing faces compared with common objects. They also found that this area was activated more strongly during the passive viewing of: intact than scrambled faces; frontal views of faces than frontal views of houses; and, three quarter view of faces than human hands. Kanwisher and colleagues concluded that the FFA is selectively involved in the perception of faces and should be viewed as a innately specialised module for face perception (232).

Activation of the right FG in response to faces has been replicated in many studies and these studies have been cited in support of its designation as the FFA (229, 233-237). Activation of the FFA has been found to be dependent on the level of attention paid to the face stimuli, and FFA activity reduced when the face stimuli appeared outside the focus of the participant's attention (238). Others have investigated right FG activation to various types of face stimuli, including animal faces, and have found that although the right FFA response was greatest for faces the right FG was also activated while viewing other percepts (239). Kanwisher and colleagues believe that individuals with face processing deficits lack innate FG specialisation as part of their disorder (232). Therefore, in the innate fusiform specialisation model in disorders such as ASD, reduced right FG activation would be attributed to the lack of innate right FG specialisation for configural processing as part of the disorder, rather than by virtue of reduced experience with facial percepts (217).

3.3.2.2 The Experience-dependant Fusiform Specialisation Model

The developmental explanation for the reduced right FG activation findings in ASD has been hotly contested between Kanwisher and Gauthier. The designation of the right FG as an innate model specialised for processing faces in typically developing individuals proposed by Kanwisher (232) has met with opposition from Gauthier and colleagues. Specifically, Gauthier and colleagues have argued that the activation pattern in the right FG in response to faces is related to experience-dependant specialisation of the right FG and expertise related to the individuals' experience with face stimuli. They have argued that activation in the right FG is secondary to sub-ordinate level processing, and that the activation reflects expertise in the processing of highly similar objects rather than faces *per se* (240).

In the model proposed by Gauthier and colleagues, there are different levels of exemplar category - the super-ordinate exemplar category is the highest-level category for an exemplar (e.g. 'furniture') and

includes basic level categories (e.g. 'tables' and 'chairs'), which in turn contain sub-ordinate categories (e.g. 'kitchen table' and 'living room table'). Most object recognition takes place at the basic level, including identifying an object as being a face as opposed to another object. Face recognition, on the other hand, takes place at the sub-ordinate level between subsets of the basic level category 'faces' (241). Gauthier and colleagues view the FG as optimal for sub-ordinate level categorisation or within-category discrimination with the important caveat that the observer is an 'expert' in the processing of that particular category of stimuli. Using fMRI, Gauthier and colleagues have investigated the effects of category level of the stimuli in a matching task of non-face objects, and found the strongest activation associated with sub-ordinate level visual recognition in the right FG for seven out of eight subjects (241). In a further fMRI study, Gauthier and colleagues used 'Greebles', a novel class of computer generated stimuli specifically designed to be similar to faces along several dimensions (242), to determine if other sub-ordinate level classes of objects would activate the right FFA (241). Interestingly when previously naïve individuals were trained to become experts in the recognition of Greebles, their recognition patterns for Greebles showed configural processing effects similar to those typically associated with face recognition, and Greebles activated the right middle FG as much as faces (243).

Gauthier and colleagues also extended this 'expertise' finding to individuals who were experts at recognition of other homogeneous categories including birds and cars. The right FFA showed higher activation in response to birds and cars than to familiar objects, and Gauthier and colleagues concluded that the level of categorisation (subordinate level discrimination) and expertise are the determining factors for activation of the right FFA rather than faces *per se* (244). Developmentally, the emotional salience of any percept is crucial to this model (245). The amygdala plays a crucial role in determining the salience of any percept such as faces in the early stage processing of facial expressions (246). Enhanced FFA activation to expressive faces has been related to amplification of the FFA activation by input from the amygdala (1). Lesions of the amygdala have been found to impair the perception of emotionally salient faces and has been associated with under activation of the FFA (247). In one study, typically developing individuals were most expert when they attributed social salience to the visual percept and individualised the stimuli (240).

Gauthier and colleagues proposed that impaired face processing in ASD individuals can best be understood using the experience-dependant right FG specialisation model rather than the innate FFA model and have challenged the notion that the FFA is a dedicated face module (187, 244). Rather they proposed that the FFA was an area engaged by any type of visual percept for which the individuals has expertise (243). Developmentally, they proposed that specialisation of the FG for the percept is experience-dependant (240), and so requires engagement with the percept.

In typical development it could be argued that the face engages individuals more than any other stimulus (248). Individuals with ASD have been found to spend less time viewing faces as they develop and faces are said to lack emotional salience in ASD. Hence, individuals with ASD are argued to not accrue typical amounts of experience with face percepts and not develop right FG expertise in the configural processing of face percepts (249). Consequently, researchers have suggested that cortical specialisation for face processing fails to develop in individuals with ASD because of their reduced social interest

(249). Individuals with ASD have also been reported to have reduced amygdala activation during face processing (167), although this has not been a consistent finding (8).

The experience-dependant right FG specialisation model would dictate that individuals with ASD should have less right FG compared to typically developing individuals during face perception tasks. The implications of the experience-dependant model for amygdala activation are less clear, as it has been suggested that the amygdala is most influential in early development and active in early in face processing (250), hence amygdala activation differences may not be apparent when individuals are older. Prefrontal cortex has been implicated in the feedback control of the amygdala in typically developing controls (250) and may also be involved in determining the social salience of faces and facial expressions (251).

3.3.3 Facial Expression Processing

A great deal of attention has concentrated on studies of face processing, in particular facial identity recognition (185, 186); however, facial expression processing may be of more relevance as an explanation for SCI in ASD (1). Face processing *per se*, and facial expression processing in particular, are important in social interaction and both the DSM-IV and ICD-10 criteria for autism and AS emphasis social dysfunction and facial expression processing deficits as features of both disorders. Hence, there is the premise in the DSM-IV and ICD-10 classification systems that there are individuals with ASD who have face and facial expression processing deficits associated with social dysfunction.

Researchers have also proposed that the atypical perceptual processing of facial expressions plays a causal role in the SCI seen in ASD (11). Several studies have reported that autistic children exhibit impairments in the interpretation of facial emotions in static images compared to typically developing children (212, 214, 252). However, not all studies have reported that individuals with ASD have facial expression processing deficits (185, 253). Indeed, a recent study reported that 'only' two thirds of the individuals with ASD studied had face processing deficits (11). This suggests that there must be also be other aetiologies for the social dysfunction in ASD, with some individuals exhibiting face processing deficits as a potential explanation for their social impairment, and other individuals with ASD having different actiologies for their social dysfunction. This aetiological heterogeneity would certainly explain some of the inconsistent facial expression processing findings to date in ASD.

3.3.3.1 Cognitive Models of Facial Expression Processing

The cognitive models of facial expression processing are, potentially, the same perceptual processing models of face processing reviewed in the previous sub-section. In effect, different facial expressions require the perceptual processing of the same facial features, but their particular configuration denotes different emotional expressions rather than different facial identity. The configuration of a face refers to the spatial relations between internal facial features, such as the distance between the eyes, and it is the interactive properties of different facial features that convey the configural information. The significance of the facial expression stimulus is rarely determined by a single distinctive feature, but rather by the particular configuration of features, and configural processing is thought necessary to recognise facial expressions (254). In contrast, there is some evidence to suggest that the processing of other aspects of

the face, such as gaze direction is insensitive to the configural aspects of facial processing and carried out in a feature-based manner using the local features around the eyes (255). Deficits in configural processing and the consequent difficulty processing facial expressions offers a possible explanation for the SCI seen in autistic individuals.

Emotional attribution from facial expression refers collectively to the perceptual, emotion and cognitive processing that enables emotions to be attributed from facial expressions. Emotion attribution involves the perceptual processing of face percepts expression, the determination of the emotional salience of the facial expression and cognitive attribution of the correct emotion to the facial expression. The attribution of emotion from facial expressions has not been studied to the same extent as face processing in ASD, despite the intuitive appeal of emotion attribution deficits as an explanation for SCI. Therefore, it remains unclear if the facial expression processing deficits are related to atypical perceptual processing of face percepts or to perceptual, emotion or cognitive deficits specifically during the attribution of emotion from facial expressions.

3.3.3.2 Functional Models of Facial Expression Processing

A previous fMRI study, which investigated the attribution of emotion from facial expression processing in typically developing individuals implicated three brain regions - the amygdala, FG, and the prefrontal cortex in the attribution of emotion in typically developing individuals (12). Accordingly, the amygdala, FG, and the prefrontal cortex regions are, potentially, relevant in understanding the attribution of emotion from static facial expressions in individuals with ASD and a brief review of pertinent literature is now given for each of these ROI.

Fusiform Gyrus

Several previous studies of facial expression in ASD have focused on determining the neural correlates associated with the attribution of emotion from different valence facial expressions (256-258), but have not investigated for an underlying perceptual mechanism common across different valence facial expressions. Until the publication of a recent fMRI study in which the hypothesis was that the FFA mediates the processing of facial identity, but not facial expression, the role of the right FG in facial expression processing was not clear. Contrary to the hypothesis, this study found that the right FFA actually showed higher activation during the processing of facial expressions in typically developing individuals. Furthermore, the FFA was sensitive to variations in facial expression even when attention was directed to identity, and showed higher activation during when the facial expression was varied, as compared to when the facial expression remained constant (259). Other studies have also shown that emotional expression boosts early visual processing of the face (260) and increased neural activation in the right FG during the viewing of the dynamic facial expressions in typically developing individuals (261).

In contrast, various studies suggest that adults with autism or AS do not demonstrate typical right FG activation when processing static facial expressions (6, 8). Although, children with autism have been reported to be better able to attribution emotion from slow dynamic presentations of facial expressions this behavioural study did not determine associated neural activation (262). To date, there have been no

studies focussing on neural activation during facial expression processing while high functioning individuals with ASD view dynamic facial expressions.

Amygdala

Brothers, who first described the 'social brain' in 1990, proposed that the amygdala was the source of empathy, and suggested that lack of empathic concern for others is a central feature of autism. Brother's model proposed that humans read evaluative attitudes and intentions from the facial expressions and eye-gaze directions of others to form a representation of the 'social situation' (263). The amygdala has since been shown to be associated with the assessment of the survival and of the emotional salience of facial expressions (264-267). Although, the amygdala is central to socially protective mechanisms through monitoring the threat of danger (268), and has been shown to be activated by both positive and negative facial expressions in healthy controls (269-271).

Hypotheses implicating amygdala dysfunction in autism have proposed that the social understanding deficit observed in individuals with ASD (272-274) is associated with reduced emotional salience of facial expressions. Individuals with ASD have been described as 'hypo-sociable,' and their SCI associated with reduced expertise in face processing and the attribution of emotion from facial expressions (275), and the use of atypical visual processing strategies (18). This in turn has been related to reduced innate social motivation and, consequent, reduced expertise in the attribution of emotion from facial expressions in ASD (240, 249).

Previous fMRI studies have found reduced amygdala activation in tasks that require the individuals with ASD to attribute the gender from neutral faces (6) and attribute emotion from static facial expressions (8). Reduced amygdala activation is also seen in high functioning individuals with ASD in tasks that require the attribution of complex emotions from only the eyes region of the face (274). However, other studies have found that high functioning individuals with ASD, who were less accurate in the explicit attribution of emotion from static facial expressions, showed relatively preserved amygdala activation (8) and that individuals with ASD who fixated on the eyes region of the face had increased amygdala activation (203). Developmental studies in monkey populations provided evidence of a critical window in development during which atypical amygdala activation may result in behavioural abnormalities that resemble autism (250). It has also recently been proposed that gaze aversion in autism effects a reduction in amygdala activation and a consequent reduction in hyper-arousal of the autonomic system (276). The later explanations may account for the mixed amygdala activation findings in individuals with autism.

Prefrontal Cortex

In typically developing individuals, the prefrontal cortex has been associated with the attribution of a mental state or TOM to another person (277, 278). Individuals with ASD have been found to have mental state or TOM deficit (279) associated with reduced activation in the prefrontal cortex (169). In a recent study high functioning individuals with ASD, who were less accurate than controls, did not have significantly different prefrontal activations when asked to explicitly attribute emotion from static facial expressions (8). The prefrontal cortex is thought to be involved in emotion processing particularly when

there is also a cognitive task involved, such as determining the response to emotional stimuli (280). Lesions of the amygdala and linked cortical areas such as the orbitofrontal cortex have been reported to impair social function (266) and cause social disinhibition (250). Studies of other neurodevelopmental disorders suggest that deficiencies in the prefrontal regulatory system, especially modulation of the orbitofrontal cortex by the dorsolateral prefrontal cortex, may result in amygdala disregulation (281).

In summary, face processing in typically developing individuals involves the configural processing of face percepts (254). Cognitive models of face and facial expression processing suggest the failure of configural processing as a possible explanation for the SCI seen in ASD. Functional models of face processing support that configural processing is supported by right FG, and include experience-dependant and innate models of right FG specialisation as potential explanations for expertise in the configural processing of face percepts. Atypical perceptual processing of facial expressions has been reported to have a causal role in the SCI seen in ASD (11). There has been an eagerness to relate the lack of perceptual expertise in individuals with ASD to their hypo-sociability and reduced expertise with faces. It remains unclear if individuals with ASD lack the capacity to configurally process faces or have the capacity to process configurally, but exhibit atypical perceptual processing such as proposed in the enhanced local perceptual precedence hypothesis (225). Amygdala and prefrontal findings during the attribution of emotion have been more mixed; therefore, the FG is of particular interest when considering the neural basis for attribution of emotion from facial expressions in individuals with ASD.

The advent of fMRI raises the possibility of identifying the neural underpinnings of SCI in ASD. The attribution of emotion from static facial expressions during the EAP has been reported to involve the right FG, amygdala and prefrontal cortex in a previous study of typically developing individuals. The EAP, therefore, offers a cognitive paradigm to investigate for atypical neural activation during the attribution of emotion in individuals with ASD. Part II of this thesis explores the cognitive and functional associations of emotion attribution from static facial expressions in individuals with ASD. The aims, rationale and hypothesis of the categorical studies are given in the next sub-sections and Chapters 4 and 5 present categorical studies of face and facial expression processing in ASD.

3.4 Aim of the Categorical Studies

To determine if atypical activation in any of the ROI involved in the attribution of emotion from static facial expressions and/ or deficits in emotion attribution represented a plausible explanation for the SCI seen in ASD.

3.5 Rationale of the Categorical Studies

Whilst reduced expertise in the attribution of emotion from static facial expressions has been acknowledged as a potential explanation for the SCI in autism (2), there has been limited previous research investigating deficits in the attribution of emotion from facial expressions as an explanation for the SCI seen in ASD. Emotion attribution from static facial expressions has been shown to activate the FG, amygdala and prefrontal cortex in typically developing individuals associated with perceptual, emotion and cognitive processing respectively (12). The hypothesis-driven ROI, chosen *a priori*, which have also previously been associated with ASD are, potentially, informative in terms of the functional

aetiology of SCI. Previous fMRI studies have found that individuals with ASD, who are hypo-sociable, have reduced right FG activation when viewing faces (6, 18). Studies have proposed that the reduced right FG activation in ASD is related to reduced experience-dependant specialisation of the right FG for configural processing of faces (7). Configural processing is required for the attribution of emotion from facial expressions, and so individuals with reduced right FG specialisation will have reduced capacity to attribute emotions from static facial expressions. The paradigms used in Studies 1 and 2 offer the opportunity to compare brain activation in FG, amygdala and prefrontal ROI during the processing of face and facial expression stimuli in individuals with ASD. Investigation of activation in the other ROI associated with the attribution of emotion from static facial expressions was also undertaken to further inform the development of an integrated explanatory model of emotion attribution from facial expressions in ASD.

3.6 Hypothesis of the Categorical Studies

- Individuals with ASD would demonstrate reduced expertise in the attribution of emotion from static facial expressions, potentially, associated with atypical neural activation in the FG, amygdala and/ or prefrontal cortex ROI.
- Specifically, right FG activation would be reduced during emotion attribution from static and dynamic facial expressions if SCI was related to atypical perceptual processing of faces in ASD, as previously reported in autism.
- Individuals with ASD would have amygdala activation abnormalities during emotion attribution from static and dynamic facial expressions if SCI was related to atypical emotion processing.
- Individuals with ASD would have prefrontal activation abnormalities during emotion attribution from static and dynamic facial expressions if SCI was related to atypical cognitive processing in ASD.

3.7 Methodology Specific to the Categorical Studies

To fulfil the aim, neural activation was measured in three ROI, previously associated with the attribution of emotion in typically developing individuals, while high functioning young men with ASD attributed emotion from static facial expressions. The categorical studies focused on high functioning individuals with HFA and AS, categories of ASD that have specific inclusion criteria. Sixteen males with a clinical diagnosis of high functioning ASD and 10 age matched typically developing males were recruited, as previously described. Qualitative and quantitative fMRI techniques were used to analyse whole brain and ROI activation associated with diagnosis during the respective paradigms. In Study 1, the FG, prefrontal and amygdala ROI previously identified to support the attribution of emotion from static facial expressions in typically developing individuals (12) were circumscribed and neural associations during the attribution of emotion in the EAP investigated. In Study 2, the neural activations associated with performance of the GAP was compared between the same individuals with ASD and same typically developing controls in the ROI identified as informative in Study 1.

Chapter 4 Study 1: Emotional Attribution from Static Facial Expressions in Individuals with High Functioning Autism Spectrum Disorders

Summary of Study 1

The FG, amygdala and prefrontal cortex have been shown to be involved in the attribution of emotion from static facial expressions in typically developing individuals (12). This study set out to determine whether expertise in the attribution of emotion from static facial expressions is reduced in high functioning individuals with ASD and if this is associated with differences in activation in the amygdala, FG, and prefrontal ROI when compared to typically developing individuals. FMRI scans were acquired from 14 males with ASD and 10 matched adolescent controls while performing the EM (perceptual), the EL (linguistic) and the control tasks presented during the EAP. Accuracy and response time were measured as indicators of expertise and activation measured for each ROI during the attribution of emotion from static facial expressions. There was no significant difference in accuracy, response time or ROI activation between groups when performing the EL task. The ASD group was as accurate as the control group when performing the EM task, but had a significantly longer response time and lower right FG activation than the control group in the perceptual task (EM), but not the linguistic task (EL). These findings provide evidence that right FG is relatively specialised for the configural processing of facial expressions in these high function individuals and that right FG hypo-responsiveness during the attribution of emotion from static facial expressions is task-dependent in these high functioning individuals with ASD.

4.1 Introduction to Study 1

Social communication involves the perceptual, emotion and cognitive processing of the facial gestures of others to attribute emotion from facial expressions (2). Reduced expertise in the attribution of emotion from facial expressions is a plausible explanation for SCI in ASD. Despite normal intelligence, high functioning individuals with ASD have marked deficits in social understanding (282). Although individuals with high functioning ASD are able to attribute emotion from static basic facial expressions (164, 253, 283-285), they have difficulty attributing emotion from more subtle facial expressions (165, 286) and facial expressions in actual social situations (287). Individuals with ASD are argued to be less expert at attributing emotion from facial expressions because faces are less salient to them (288) and as a consequence they are assumed to accumulate less experience with faces (249). Many of the deficits in social cognition seen in ASD are consistent with reduced expertise in the attribution of emotion from facial expressions (289, 290). Individuals with ASD may be less expert by virtue of being less accurate in the attribution of emotion, but also may be less expert by responding slower than typically developing individuals (291). Therefore, both accuracy and response time were measured, as both are important measures when considering expertise in the attribution of emotion from facial expressions in ASD.

The attribution of emotion from static facial expressions has been studied in typically developing individuals by Hariri and colleagues using the EAP, which incorporates an EM task and an EL task. The EM task involves the attribution of emotion from three static facial expressions and a visual match of emotion, whereas, the EL task involves the attribution of emotion from one basic facial expression and affective labelling of the emotion from two given emotion labels. The EM task involves greater perceptual processing and there are no emotion labels; therefore, there is no language facilitation in this task. The EL has a lower perceptual processing load and has emotion labels, which may provide language facilitation during the attribution of emotion from the presented facial expression. In typically developing individuals, the attribution of emotion was found to significantly activate the amygdala and fusiform regions in the EM task, and the FG and prefrontal regions in the EL task, of the EAP (12). The amygdala, FG and prefrontal ROI have also previously been implicated more broadly in typical and atypical social development. Accordingly, these brain regions are potentially relevant in understanding the attribution of emotion from static facial expressions in typical development and individuals with ASD. Whilst reduced expertise in the attribution of emotion from facial expressions has been acknowledged as a potential explanation for the SCI in autism (1), there have been no previous studies of the neural associations with emotion attribution from facial expressions in high functioning individuals with ASD.

4.2 Aim of Study 1

The aim of Study 1 was to identify any atypical neural activation associated with the diagnosis during the attribution of emotion from static facial expressions in individuals with ASD compared to typically developing individuals.

4.3 Rationale of Study 1

The processing of faces and facial expressions is central to social communication, and reported as impaired in individuals with ASD (292). Reduced expertise in the attribution of emotion from facial expressions offers a potential explanation for the SCI seen in ASD. Specifically, reduced right FG specialisation for configural processing of facial expressions has been postulated as a potential explanation for reduced expertise in the attribution of emotion from facial expressions (240) and SCI seen in ASD (1). Opinion is divided; some consider right FG specialisation for faces to be innate, while others advocate experience-dependent right FG specialisation for the perceptual processing of faces related to social motivation. Individuals with ASD offer a unique opportunity to study the neural activation in three ROI, known to be active during the emotion attribution from facial expressions, in a group of individuals, who are characteristically hypo-sociable and assumed to have accrued reduced experience with faces.

4.4 Hypothesis of Study 1

- High functioning individuals with ASD will demonstrate reduced expertise and reduced right FG activation during the attribution of emotion from static facial expressions in both the EL and EM task of the EAP.
- When compared to typically developing individuals, amygdala activation in the EM task may be atypical in high functioning individuals with ASD, related to reduced expertise in the attribution of emotion from static facial expressions and/ or SCI in high functioning individuals with ASD.
- Prefrontal activation in the EL task may be atypical when compared to typically developing individuals, related to reduced expertise in the attribution of emotion from static facial expressions and/ or SCI in high functioning individuals with ASD.

4.5 Methodology Specific to Study 1

To address the aims of the study, 16 high functioning individuals with ASD and 10 typically developing individuals were recruited, as previously described, for participation in the categorical studies. These participants attributed emotion from static facial expressions presented in the EM and EL tasks during the EAP while fMRI data was acquired on a 3 Tesla GE scanner. The EAP allowed investigation of the FG, amygdala and prefrontal cortex ROI, previously implicated in the attribution of emotion from static facial expression in typically developing individuals. Neural activation was measured in the FG, amygdala and prefrontal cortex ROI during the EAP to determine if there were activation differences in these three brain regions between high functioning individuals with ASD and typically developing control individuals that could account for the SCI in those with an ASD diagnosis.

4.6 Results of Study 1

4.6.1 Behavioural Measure Results

16 males with high functioning ASD diagnosed using DSM-IV (25) and 10 male control subjects were recruited. All high functioning individuals with a clinical diagnosis of ASD fulfilled the ADOS-G (21) criteria for the broader ASD, and those with a clinical diagnosis of autism also fulfilled criteria for autism using the ADI-R (20). The high functioning ASD group consisted of eight individuals with autism and

eight individuals with AS. Two high functioning males with ASD were excluded from the analysis because their brain scans had too much movement to analyse: one from the HFA; and, one from the AS group. These two high functioning males with ASD were not significantly different from the high functioning males with ASD who were included in the analysis.

4.6.2 Demographic and Neuropsychological Results

The ethnicity of the ASD group was nine Caucasian, three Asian and two Hispanic individuals and the control group was seven Caucasian, one Asian and two Hispanic individuals. The ASD and the control groups were both of high socio-economic status. In the ASD group: two individuals had anxiety disorder and were receiving serotonin reuptake inhibitors; two individuals had ADHD and were receiving methylphenidate; and, one individual in the ASD group, who had both anxiety and ADHD was receiving both of these medications.

14 high functioning males with ASD (mean age = 13.1, SD = 2.5, range = 9-17 years), and 10 male control subjects (mean age = 14.4, SD = 3.3, range = 10-18 years) had usable scans and were included in the analysed. The high functioning ASD group consisted of 7 individuals with HFA and 7 individuals with AS. Independent samples *t*-test showed no significant difference in age [$t(22) = -0.99$, $p = 0.33$] or IQ [FSIQ: $t(22) = 0.633$, $p = 0.53$; VIQ: $t(22) = -1.26$, $p = 0.22$; PIQ: $t(22) = 0.897$, $p = 0.328$] between the two groups. The ASD group [FSIQ = 112, SD = 15.9; VIQ = 104, SD = 20.3; PIQ = 118, SD = 13.6] and the control group [FSIQ = 116, SD = 10.5; VIQ = 114, SD = 14.2; PIQ = 114, SD = 6.3] had average to above-average cognitive function. All subjects were right-handed [ASD = 87%, SD = 13.0%; control = 82.3 %, SD = 15.3%] as assessed by the EHI (293).

Figure 4-1 Accuracy in the Emotion Attribution Paradigm

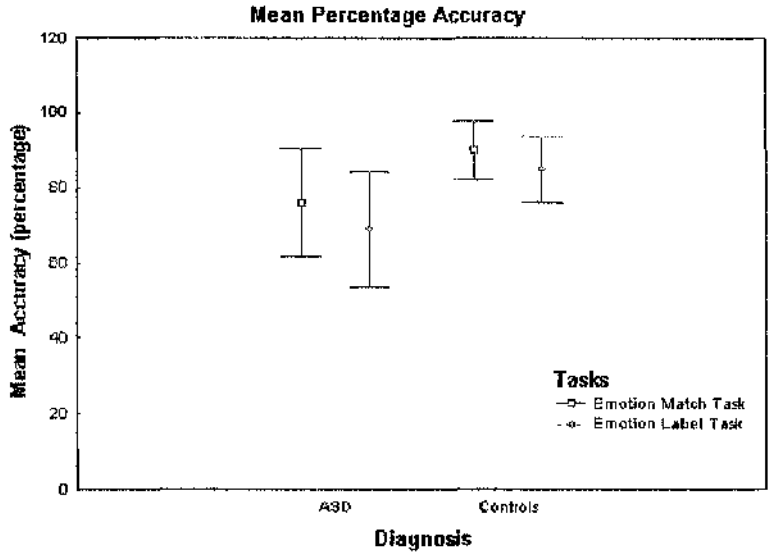


Figure 4-1 shows no significant difference in accuracy between the ASD and control group in the emotion match and emotion label tasks in the Emotion Attribution Paradigm (1 SD from the mean is shown for each task).

There was also no significant difference in accuracy between groups in the EM [$t(22) = -1.626$, $p = 0.118$; ASD mean = 76%, SD = 25%; control mean = 90%, SD = 11%] or the EL task [$t(22) = -1.768$, $p = 0.095$; ASD mean = 69%, SD = 27%; control mean = 85%, SD = 12%] (Figure 4-1). There was a significant difference between groups in response time in the EM task [$t(22) = 3.33$, $p = 0.003$; ASD mean = 2531 sec, SD = 393; control mean = 2047 sec, SD = 272]. There was no significant response time difference between groups in the EL task [$t(22) = 0.623$, $p = 0.539$; ASD mean = 2141 sec, SD = 363 sec; control mean = 1960 sec, SD = 300 sec] (

Figure 4-2). Accuracy and response time were incorporated as covariates into the ANCOVA model to remove the variance attributable to expertise and ascertain the average activation attributable to diagnostic group.

Figure 4-2 Response Time for the Emotion Attribution Paradigm

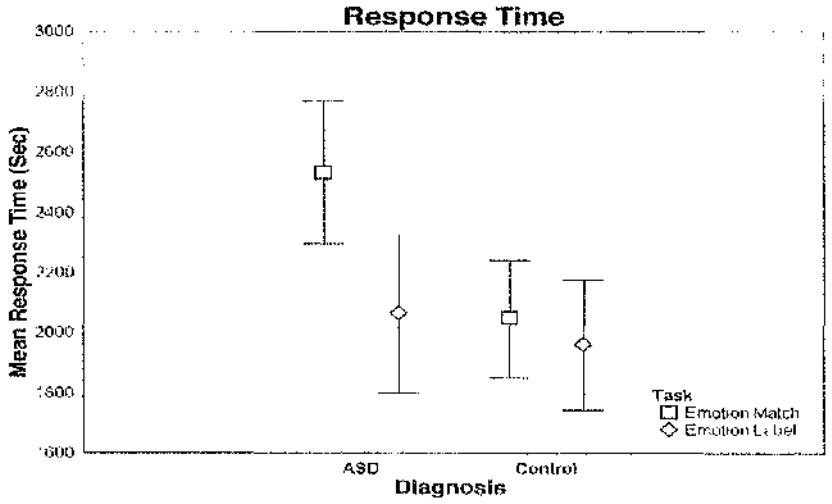


Figure 4-2 shows a significant difference in the mean average response time between the ASD and control group in the emotion match task, but not the emotion label task in the Emotion Attribution Paradigm (1 SD from the mean is shown for each task).

4.6.3 Regions of Interest Analysis Results

4.6.3.1 Amygdala

ANCOVA indicated that there was no significant difference in the average amygdala activation between groups in the EM [$F(1, 22) = 3.39$, $p = 0.56$] or EL [$F(1, 22) = 1.81$, $p = 0.198$] tasks.

4.6.3.2 Fusiform Gyrus

ANCOVA indicated that there was a significant difference in average right FG activation [$F(1, 22) = 12.02$, $p = 0.003$] between groups in the EM task. There was significantly less average right FG activation in the ASD group (mean = 2.13, SD = 0.32) than in the control group (mean = 2.61, SD = 0.31) (effect of covariate: response time: [$F(1, 22) = 8.8$, $p = 0.008$]. There was no significant difference

in average right FG activation [F(1, 22) = 0.111, p = 0.743] between the ASD (mean = 2.52, SD = 0.33) and the control (mean = 2.47, SD = 0.34) group in the EL task (Figure 4-3).

Figure 4-3 Right Fusiform Gyrus Activation for Emotion Attribution Paradigm

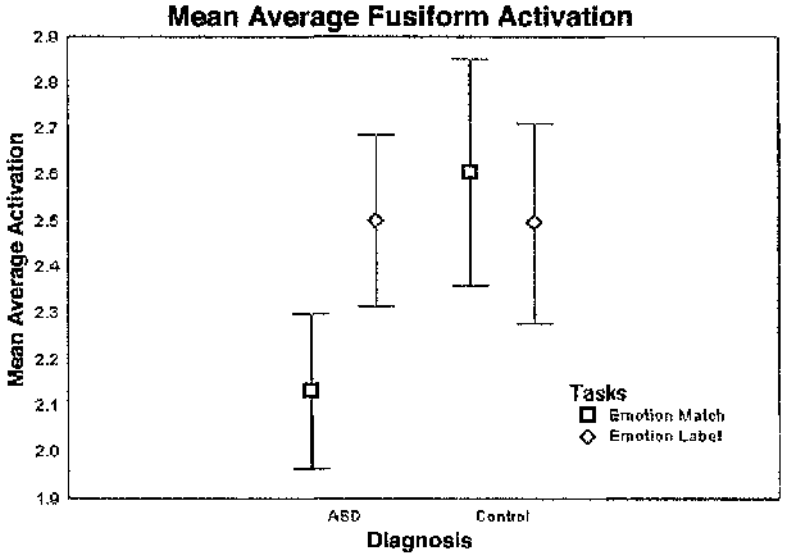


Figure 4-3 shows a significant difference in the mean average right fusiform gyrus activation between the ASD and the control group in the emotion match task, but not in the emotion label task in the Emotion Attribution Paradigm (1 SD from the mean is shown for each task).

4.6.3.3 Prefrontal Cortex

ANCOVA indicated that there was no significant difference between groups for average prefrontal activation in the EM [F(1, 22) = 0.028, p = 0.87] or the EL [F(1, 22) = 0.086, p = 0.772] tasks.

4.7 Data Interpretation 1

The ASD and the control groups had comparable accuracy (Figure 4-1) and response times (Figure 4-2) and thus, expertise on the EL task. Comparison of different brain activations is facilitated when both groups are able to perform the task, ideally to a comparable level (39). Comparison of neural activation in the EL task found no significant difference in neural activation in any of the three ROI between the ASD and the typically developing individuals. This finding was contrary to the prediction of reduced right FG activation in this emotion attribution task, and supports the notion that high functioning individuals with ASD are as expert as typically developing individuals when attributing emotion from a single face when the stimulus is presented in a language-facilitated (EL) paradigm.

The equivalent right FG activation in the EL task indicates that the right FG is involved in attributing emotion from static facial expressions in both the ASD and typically developing control groups. Another plausible explanation for the comparable right FG activation is that both groups used configural processing to attribute emotion from the basic facial expression stimuli in the EL task, and suggests that high functioning individuals with ASD have functional right FG. The presentation of a single facial

expression and affective labels may have facilitated expertise in the attribution of emotion in the EL task. In addition, in the EL task there was no control for the labelling of static facial expressions. Potentially, the label may have facilitated the attribution of emotion. It has been suggested that individuals with AS may utilise compensatory strategies, such as verbal mediation, to process facial expressions of emotion. The comparable right FG activation between the ASD and typically developing control group may have been related to the reading of the affective labels in the EL task, and not to the visual processing of a face percept. However, letter-strings have been shown to activate nearby areas such as the occipitotemporal and inferior occipital sulci (235), not the right FG *per se*.

However, high functioning individuals with ASD were less expert in the attribution of emotion from static facial expressions in the EM task of the EAP. Specifically, the ASD group had equivalent accuracy, but significantly longer response time, than the control group in the EM task. Differing expertise in the EM task potentially confounds the interpretation of brain activation (294); therefore, accuracy and response time were covaried to determine the ROI activation attributable to diagnostic group. This finding supported the prediction that high functioning individuals with ASD would have less expertise in the attribution of emotion from facial expressions; however, in the EM task only. The ASD group also had comparable amygdala and prefrontal activation, but significantly reduced right FG activation, compared to the control group in the EM task (Figure 4-3). Response time did not explain the reduced right FG activation in the ASD group in the EM task. Individuals with ASD have previously been reported to have reduced right FG activation when processing facial stimuli (6, 18). Reduced expertise in the perceptual (EM) task may be explained by the absence of affective labels and/ or the increased number of facial stimuli constituting an increased configural processing load. Individuals with ASD have been suggested to have reduced expertise in the configural processing of facial stimuli (249) and during the processing of facial stimuli to activate the FFG, an area associated with feature-based analysis of objects (18). The use of a feature-based visual strategy supported outside the right FG offers a possible explanation for the reduced performance and reduced right FG activation when individuals with ASD attribute emotion from static facial expressions in the perceptual (EM) task. One possible explanation for the EM finding is that high functioning individuals with ASD, although able to attribute emotion from basic facial expression, do so only when this is a necessary and explicit aspect of the task, and otherwise have a preference/ predisposition toward feature-based visual processing of facial expressions. Another possibility is that high functioning individuals with ASD use a different cognitive strategy when faced with an increased visual load to configurally process. Recent studies would also suggest that the reduced right FG activation is related to reduced attention to the eyes region of the face (9). Therefore, the reduced right FG activation in the EM task may be secondary to decreased attention to the eyes region of the face during the matching of emotion attribution between facial expressions in this task. This requires further investigation and will be addressed in the next study.

Activation in the amygdala and prefrontal regions of high functioning individuals with ASD were comparable to that of typically developing individuals for both the EL and the EM tasks. Studies have reported increased amygdala activation, related to fixation on the eyes region of the face, and have suggested that individuals with ASD may avert their gaze from the eyes region of the face in the EM task

to reduced arousal mediated via the amygdala (203). Studies have also reported reduced prefrontal activation in ASD related primarily to TOM processing tasks (169). However, the most similar study to date found no significant differences in amygdala and prefrontal activation when high functioning individuals with ASD were explicitly instructed to attribute emotion from static facial expressions (8). Previous studies that have shown reduced prefrontal (169) and reduced amygdala (6, 8, 274) activation did not involve the explicit attribution of emotion from static facial expressions. In these studies, there were also differences in performance between groups that potentially could have explained the observed profiles of activation.

4.8 Key Findings of Study 1

Expertise in the attribution of emotion from static facial expressions was task-dependent in individuals with ASD. Previous studies of typically developing individuals have reported that patterns of cerebral activation are dependent on the requirements of the face processing tasks (295). The integrity of the right FG when attributing emotion in the EL task suggests that the right FG is relatively specialisation for face processing, despite hypo-activation of the right FG in the during the EM task in individuals with ASD. The task-dependant right FG activation during the attribution of emotion from static facial expressions provides support for configural processing in ASD. Explanation of the task-dependant difference in expertise in the attribution of emotion in the ASD group requires further consideration of the: differences in task demands; differences in predisposition/ preferences in visual style; and, differences in degree of attention to the eyes region of the face. These areas will be further explored in subsequent studies.

4.9 Methodological Considerations of Study 1

The following methodological issues with respect to subject recruitment, behavioural measure, paradigm design and procedure, image pre-processing and ROI processing need to be taken into account when considering the findings of this study.

4.9.1 Subject Recruitment

The sample size in this study was relatively small, and may have reduced the power of the study to detect significant differences between groups. This is of particular relevance when considering the null findings for amygdala and prefrontal regions during the attribution of emotion from facial expressions. However, the sample size was comparable to, and in some cases greater than, samples reported in previous studies of face and emotion processing in autism (6, 18). Power calculations for fMRI studies is an area of intense research and will allow for appropriate powered fMRI sample sizes in future studies.

The recruitment of high functioning individuals by advert from the locale means that the findings are not generalisable to the population. However, these high functioning individuals with SCD were recruited because they represent an understudied group and were well characterised to facilitate interpretation of the findings from the studies. However, it should be noted that sample bias can be introduced by any systematic error that results in an incorrect estimate of the association, in this case between brain activation and task performance in the ASD and the control groups. Therefore, different sampling strategies would be beneficial for fMRI study such as: ascertainment from a representative sample of the ASD population; selection of a homogeneous ASD subgroup; or, selection a heterogeneous ASD group

and measurement of the variability in performance as seen in a recent fMRI study (203). The latter approach will be utilised in Study 4.

The high functioning individuals with ASD recruited for this study were not recruited from a representative sample of the population as suggested above, and there are ascertainment biases introduced by clinician referral, individual clinician diagnostic practices, and participation bias such as self-selection (volunteerism). The biases in this study include the greater participation of higher socio-economic groups, most of whom were from a particular geographical location within the catchment of the study. Biases, when present, have been addressed by: having a clear definition of the study population - including explicit ASD and control criteria; selecting the ASD and control groups from same population; and, clearly characterising the participants recruited. The characteristics of the participants are well documented in the publications emanating from this study (296).

In the recruited sample, some individuals with ASD were receiving medication for co-morbid disorders. Individuals on medication were included in this study as their medications were prescribed for symptoms other than SCI. These medications may, however, have influenced brain activation patterns, but it is difficult to ascertain medication naïve individuals and unethical to stop medication for fMRI study. The findings of this study ideally need to be replicated in individuals with ASD that are medication naïve.

The ASD sample consisted of seven individuals with HFA and seven individuals with AS, therefore, half of the individuals in the ASD group had a history of delayed language at the age of three and half had no history of language delay. Prior to the combination of these two diagnostic groups, analyses were undertaken to ensure that there were no substantial differences in current language skills or detectable differences in performance or brain activation between the individual with AS and HFA in the EM or EL tasks. However, the small size of AS and HFA groups may have meant that although differences were actually present between groups they were not detected.

Individuals with a known aetiology for their SCI (e.g. fragile X, tuberous sclerosis, rubella) were excluded from this study. Exclusion is based on the assumption that these disorders do not have the same underlying neurobiology for any exhibited SCI. However, no studies have focused on comparing performance and brain activation on measures of SCI between individuals with ASD and individuals who have a known aetiology for their SCI. Both groups may actually have a common neurobiological aetiology despite differences in underlying genetic aetiology and this approach may inadvertently decrease the power.

In this study, the groups were matched for IQ and age, and limits set on the age and IQ range of the individuals recruited. Matching IQ and age at the group, rather than individual level, may have reduced the power to detect differences in performance in the EAP between the ASD and typically developing groups. It is optimal to control for differences between ASD and control groups, such as IQ and age, by optimising study design and matching individuals prior to data collection. The most stringent match would involve pairing the ASD and the control individuals. This would have increased the power to detect the difference between groups related to the variables of interest, and allowed the use of paired t-

test in the statistical analysis. Future studies should attempt this more stringent matching between groups.

4.9.2 Behavioural Measures

There are several diagnostic and behaviour measurement considerations in this study. The ADI-R primarily focuses on diagnostic criteria for autism and does not diagnose other PDD such as AS and PDD-NOS. Individuals with SCI, who did not fulfil criteria for autism, were recruited into this study if they fulfilled ADOS-G criteria for the broader PDD classification. ADOS-G has 'cut-off' scores for the broader diagnosis of PDD, as well as the traditional, narrower conceptualisation of autism. The use of the standardised 'play' materials and standardised ratings that constitute the ADOS-G gives a measure of ASD that is unaffected by language. All individuals in this study fulfilled ADOS-G criteria for broader PDD, a definition that is used interchangeably with ASD. Both ADI-R and ADOS-G are categorical assessment instruments that rate symptoms as sufficient for a diagnosis when the symptoms are above a certain threshold. Below this cut-off, individuals with qualitatively and quantitatively similar deficits are rated as unaffected. Neither of these instruments were designed to measure severity and, hence, the severity of autistic symptomatology was not directly measured in the individuals with ASD that participated in this study. Therefore, the relationship between neural activation and severity of SCI, although of great interest, could not be determined in the current study.

Although the ADI-R was used in this study to identify those with HFA, it does not diagnose AS. There is no standardised diagnostic instrument that diagnoses both HFA and AS. High functioning individuals with SCI, who have no history of language delay, have often been excluded from studies to reduce diagnostic uncertainty (66). There is much debate as to whether AS is a separate diagnostic entity to HFA (297); however, qualitatively both HFA and AS can have similar SCI. In this study, in line with the National Institute of Health Collaborative Programs for Excellence in Autism guidelines, ADI-R/ ADOS-based DSM-IV (APA, 1994) diagnosis of ASD were made, which facilitates the inclusion of individuals with AS (298). However, individuals with PDD-NOS were excluded from Study 1, despite having qualitative and quantitatively similar SCI, and this will be addressed in subsequent studies.

The ADI-R is a parental report and individuals are deemed to fulfil a diagnosis of autism based on parental recall of the child's behaviours between 4–5 years of age. Therefore, to complete the ADI-R parents are, in effect, asked to recall children's behaviours from at least 5 years and up to 13 years before, which undoubtedly introduces bias in parental report. The ADI-R is a semi-structured interview, which relies on the interviewer determining the coding for the behaviour based on a conceptual understanding of autism developed during training with the instrument. However, intra-rater and inter-rater reliability is difficult to establish and maintain, and affects the reliability of ADI-R diagnosis. ADOS-G is an observational instrument, and intra-rater and inter-rater observer bias can occur in the ADOS-G. Despite these potential biases, without the identification of an objective measure of ASD (such as a biological marker), the completion of both these 'gold standard' measures represents current best diagnostic practice for a diagnosis of ASD in research settings.

This study investigated for group differences in performance between ASD and typically developing individuals during the attribution of emotion from static facial expressions. No attempt was made to measure the performance of the individuals during the attribution of emotion from static facial expressions prior to the fMRI experiment. Undoubtedly, individuals with ASD are a heterogeneous group; therefore, the average neural activation from the individuals with ASD represents activation from a group of individuals with ASD, some of whom will not have deficits in emotion attribution from facial expressions. An alternate approach would have been to select for emotion attribution or face processing deficits and ASD. Identification of individuals with ASD and emotion attribution or face processing deficits, and quantification of these deficits would have been a potentially more informative approach to the identification of the neural correlates of SCI in ASD and is addressed in subsequent dimensional studies.

4.9.3 Paradigm Design and Procedure

Ideally, a concurrent, observable, and measurable behavioural response such as a yes or no button-press should be used to verify task performance in the scanner (299). This study used both accuracy and response time to ensure that subjects performed the task, and to gather information on cognitive strategies from behavioural performance. However, participants can obviously be more accurate by responding more slowly, and can forfeit accuracy and respond more quickly by being less accurate. Given the impact of speed/ accuracy decisions, it is surprising that the basic processes underlying these decisions are still poorly understood. The psychological literature generally treats speed/ accuracy decisions as involving a built-in trade-off, people either trade speed for accuracy or vice versa. Speed/ accuracy decisions are also influenced in part by the strategic inclinations of participants as opposed to a built-in trade-off (291). Self-regulatory accounts of behaviour in speed/ accuracy tasks are emerging, which involve strategic influences on speed/ accuracy decisions such as regulatory focus (300). Future studies need to perform psychometric analysis to better understand the trade-off between accuracy and response time in neurocognitive tasks. Studies are also needed to determine if a composite neurocognitive measure such as expertise, which takes account of this trade-off, has utility. Alternatively, studies should be undertaken to determine if accuracy and response time do represent different cognitive or functional strategies, as suggested recently in fMRI vision research (301) and, confirm that they need to be analysed separately as in this study.

Studies investigating the differences in brain activations between ASD and typically developing individuals are best placed to do so when both groups can perform the task, and behavioural performance is comparable between groups (39). When groups are unable to perform the task, it becomes unclear how the neural activation relates to CCI; therefore, the capacity to perform the task at a similar level of competency aids the interpretation of fMRI results. Yet it is difficult to ensure similar levels of performance in any neurocognitive experiment. Many experiments taken from behavioural psychology are actually designed to ensure differences in performance, and these differences are considered informative in behavioural experiments. When comparing neural activation, differences in performance variables such as accuracy and response time can be statistically incorporated as covariates. Statistical advice supported the presentation of ANCOVA with response time and accuracy as covariates in the EM

task in this thesis. However, the effect of performance differences on neural activations is unclear and incorporation as a covariate, although statistically appropriate, may not be biologically meaningful.

In fMRI experiments, to determine that neural activation related to the CCI, the cognitive constructs that are inherent, but not of interest, need to be controlled for in the design of the paradigm. Two levels of control task are used in the fMRI experiments and dependent upon the degree of similarity to the experimental task, referred to as tight (high degree of similarity) and loose (low degree of similarity) control tasks. A tight control task should consist of all cognitive constructs present in the experimental task except for the CCI, and isolate the latter. In contrast, loose control tasks only control for very basic cognitive processes, so when the experimental and control task are compared an entire network of areas active specifically in support of the experimental task are activated. The EAP had a very basic control and so in terms of interpretation it was not possible to attribute the brain activation to specific CCI (302).

In this study, a very basic control task was used as the baseline, to enable comparison of both experimental tasks. Rest and fixation can also be used as baselines when determining the activation related to the experimental task, but subjects often undertake other cognitive processes while they rest or fixate introducing activation error. A very basic visual or loose control task, which involved the visual match of geometric shapes, was used in this study as a baseline to allow the comparison of both the EM and EL tasks in the EAP. The subtraction of the brain activation associated with the loose control task from the brain activation associated with the experimental task subtracted the brain activation associated with basic visual processing and matching of shapes. All remaining brain activation was related to all other aspects of performance of the respective experimental task. In the EL task, activation was associated with the processing of faces, the attribution of emotion and the match of the emotion from one basic facial expression with the correct linguistic label. In the EM task, activation was associated with the processing of faces, the attribution of emotion and the match of the emotion from one of two basic facial expressions with the same facial emotion as the target face. The use of a loose control meant that it was not possible to determine if the atypical neural activations were related specifically to the attribution of emotion from static facial expressions or to some other aspect of face processing inherent the task.

A block design was used in this study in which blocks of the EM task were alternated with blocks of the EL during the EAP. This is a common experimental paradigm presentation approach, but can be problematic as differential patterns of neural activity can be specific to the block, rather than the experimental tasks, and not related to the CCI. Block design experiments are prone to confounding activation and this is a known shortcoming of this design. This confounding activation can occur, for example, in the first block if the subject is anxious just after they have entered the scanner or in the last block if the subject is fatigued at the end of a scan. Introduction of a rest period at the beginning and end of the experiment and presentation of a block of the control task in the first block reduce the potential impact. In this study, participants underwent a behavioural fMRI desensitisation program and fMRI simulation to acclimatise them to the fMRI environment and reduce confounding influences. Another shortcoming of block design experiments is that brain activation associated with accurate responses cannot be separated from inaccurate responses. When comparing brain activation it is optimal to

compare activation associated with accurate performance of the task, because accurate performance infers that the individual is performing the task. Event-related experimental designs can be used to isolate extraneous factors and separate brain activation from accurate and inaccurate responses, avoiding some of the problems of analyzing and interpreting data from block designed (303).

4.9.4 Imaging Pre-processing

FMRI offers the opportunity for non-invasive in-vivo measurement of structure-function relationships in the human brain. FMRI measures neural activity indirectly through oxygen changes in the blood (304). Increased blood flow occurs in areas of neural activation and results in decreased deoxyhaemoglobin in the blood, which conveys a signal commonly referred to as the BOLD contrast signal, which is detected by MRI. The blood flow is known as the HRF, and although not directly coupled is taken as a proxy measured of neural activity. Early studies, using sustained stimulation paradigms, showed that the HRF is delayed in onset from the time of presumed neural activity by about 2-6 seconds (304), and prolonged in duration, lasting in order of 10-12 seconds beyond the neural activity (305). Explicit models of HRF have been incorporated in the analysis of fMRI time series (analysis which tracks the brain activation in a specific brain area over time) data in order to better account for the response lag and delayed offset properties of the BOLD HRF (303), within the statistical framework of the GLM (306). Explicit models for the BOLD response are present in SPM99 (43); however, studies have shown that there are differences in haemodynamic BOLD responses in different areas of the brain (307, 308) and considerable variability in HRF between subjects (309). The study presented did not look at individual HRF, and instead used a generic model that assumed the same HRF signal for all brain regions. Generic HRF models only account for about 70% of the variance in HRF, whereas, subject specific models can explain up to 92% of the variance in HRF. Future studies should model individual-specific HRF to count for more of the variance, and correlate individual and brain region specific HRF with task performance.

4.9.5 Region of Interest Processing

The hypothesis-driven nature of this study and identification of ROI *a priori* are both strengths and potential weaknesses of this study. ROI analyses allowed investigation for quantitative differences in brain regions known to be involved in the attribution of emotion in typically developing controls (310) and the identification of ROI *a priori* allowed for a directed hypothesis. The research question in this study related to the difference between the ASD group and typically developing controls in these ROI identified *a priori*. The hypothesis and selection of ROI *a priori*, reduced the number of multiple comparisons, and increased the power to detect differences between groups. WBA would have identified the voxels that were significantly activated by the ASD group during the emotional attribution paradigm throughout the whole brain. However, WBA was not undertaken because the study design was hypothesis-driven and based on ROI identified during the study of emotional attribution from static facial expressions in typically developing individuals (12). Anatomically defined ROI are defined using structural, as opposed to functional boundaries (311). The reliability of these boundaries depends on how discernible the sulci between gyri are on the structural images, and the expertise of the individual who draws them (312). For some ROI the boundaries are easily identified and can be reliably drawn. Other ROI are not easily identified and there is considerable intra-subject and inter-subject variability, even

between experts, when they are drawn. The benefit of anatomically defined ROI approach used in this study is that the boundaries can be described and compared across studies. The time consuming nature of defining subject-specific ROI manually represents a 'research' speed/ accuracy trade-off. In this study, group-specific ROI for the ASD and the control groups were defined on averaged group anatomical images. Inter-subject anatomical variability and whole brain spatial normalization can make boundaries difficult to delineate; however, to facilitate the delineation of boundaries in the group image, a high quality anatomical image called a SPGR image was acquired. Future studies using semi-automated methods to defined subject-specific anatomical ROI would allow for a better measure of the inter-subject anatomical variability while exploring hypotheses in specific brain regions (313).

4.10 Conclusions and Implications of Study 1

The hypothesis that individuals with ASD would have reduced right FG activation during both the EM and the EL tasks of the EAP was partially upheld. Individuals with ASD did have reduced right FG activation when compared to typically developing individuals during the EM task, but contrary to the hypothesis individuals with ASD had comparable right FG activation to typically developing controls in the EL task. This provided evidence that reduced right FG activation in the EAP was task-dependent in individuals with ASD that participated in this study. These findings provide evidence for comparable cognitive and emotion processing and task-dependant atypical perceptual processing during the attribution of emotion from static facial expressions in ASD.

Task-dependent differences in right FG require consideration of the inherent differences between the EL and EM tasks in the EAP. In the EL task, individuals with ASD may have successfully completed the task using linguistic facilitation provided by the affective labelling presented below the face. Differing perceptual strategies may have been necessary in the EM task: to negotiate the increased perceptual processing of three faces; the increased emotion attribution from three facial expressions; or, reduced linguistic facilitation when compared with to the EL task. Individuals with ASD could have successfully completed the EM task using feature-based processing without attributing emotion from the static facial expressions. To determine if reduced right FG activation in high functioning individuals with ASD is related to the attribution of emotion from facial expressions, or to face processing *per se*, requires: the same group of individuals to undertake a face processing task; the use of a tighter control task; and, the use of an experimental task that requires attention to the eyes region of the face. Therefore, a further study using a more basic face processing paradigm was used in the same group of young men in Study 2. The GAP was presented in a block experiment design to determine brain activation during the implicit processing of neutral faces and did not require attribution of emotion from facial expressions. Each stimulus consisted of a single neutral face without linguistic labels, thus addressing the confounds present in the tasks in the previous EAP (296). The GAP also required attention to the eyes region of the face to attribute the direction of gaze and incorporated scrambled faces, providing a tight control for all cognitive constructs other than face processing. Therefore, the design of the GAP provided a robust test of competing hypotheses to account for reduced right FG activation in individuals with ASD.

Chapter 5 Study 2: Gaze Attribution from Neutral Faces in High Functioning Individuals with Autism Spectrum Disorders

Summary of Study 2

Several imaging studies have reported that individuals with ASD have reduced or absent right FG activation during face processing tasks compared to typically developing individuals (6, 18, 314). Recent imaging studies have reported that right FG activation is related to attention to the eyes region of the face in ASD (315) and comparable to typically developing controls when individuals with ASD attended to emotionally neutral faces (9). This study set out to determine if individuals with ASD, who had reduced right FG activation during an face processing task in a Study 1 (296), would have comparable right FG activation to typically developing control group in a task that required them to attend to the eyes region of emotionally neutral faces. FMRI data was acquired from 16 males with ASD and 10 age and gender matched controls during the GAP. There were no performance differences between the groups in the GAP and WBA revealed that both groups activated the right FG, although the ASD group activated the right FG less than the control group. ROI analysis confirmed that the ASD group had significantly less right FG activation than the control group. Hence, reduced right FG activation persisted in this group of high functioning individuals with ASD despite attending to the eyes region of emotionally neutral faces. However, this task could also have been successfully performed using feature-based analysis and, therefore, enhanced local perceptual precedence could account for the reduced right FG activation in individuals with ASD. Future studies to determine right FG responsiveness during the processing of face/ facial expressions in individuals with ASD should utilise paradigms that require continuous attention and necessitate the configural processing of the face/ facial expression stimuli.

5.1 Introduction to Study 2

Various studies support the notion that SCI as seen in autism is related to atypical face processing strategies such as reduced attention to the eyes, increased focus on the mouth (186, 205), and abnormal visual scan patterns (17) characterised by a decreased tendency to look at the inner features of the face (205, 315, 316). Indeed, high functioning individuals with ASD have been reported to use a feature-based strategy for face processing (290), which reportedly supports superior performance in visual search tasks, but inferior performance on face processing tasks (17). Consistent with the feature-based perceptual processing of faces, high functioning individuals with ASD have been reported to have reduced activation in the right FG, an area normally activated by typically developing individuals when processing emotionally neutral faces, and increased LTG activation, an area activated by typically developing individuals when processing objects (18). Absent right FG activation has also been reported in high functioning individuals with autism when viewing emotionally neutral faces (6), and reduced accuracy and reduced right FG activation observed when high functioning individuals with ASD labelled emotions presented on emotionally expressive faces (314).

In contrast to the findings described above, the results from Study 1 showed that during a face processing experiment that required matching one of two emotion labels to an emotionally expressive face (the EL task), high functioning individuals with ASD had comparable task performance and right FG activation to typically developing controls. When compared to controls on a task that involved matching one of two facial expressions with a target face expression (the EM task), these same individuals with ASD demonstrated longer response time and reduced average right FG activation. Taken together, these findings highlight the performance and activation differences that can occur in the same group of individuals with ASD when task demands are altered within the cognitive domain of emotion attribution. More fine-grained analysis of the EM task specific reduction in right FG activation in the ASD group indicated that this finding was not explained by longer response time. Rather, these analyses suggested that task-dependent differences in right FG activation in the ASD group required consideration of the inherent differences between the EL and EM tasks.

However, recent studies have also suggested that reduced gaze fixation on the eyes region of the face is associated with hypo-activation of the right FG in individuals with autism (203), and reduced right FG activation directly related to length of gaze fixation on the eyes region. Accordingly, reduced right FG activation in the EM task, as well as in other face and emotion studies of ASD could be explained, in part, by reduced attention to the eyes region of the face by individuals with ASD. Consistent with this hypothesis, another recent imaging study, in which eleven individuals with HFA and ten typically developing individuals were required to attend to a fixation cross in the centre of an emotionally neutral face, showed no group differences in right FG activation. These findings raise the possibility that reduced right FG activation is related to attention to face percepts and that the right FG is not a critical component of the face processing impairment in autism (9). Therefore, in this study, Study 2, the GAP was used to address the confounds present in the EAP in Study 1 and investigate if individuals with ASD have reduced right FG activation related to implicit face processing during gaze attribution from neutral faces.

5.2 Aim of Study 2

The aim of this study was to determine if high functioning individuals with ASD, who had reduced right FG activation in the EM task of the EAP, activated the right FG when attributing the direction of gaze from neutral faces in the GAP to a comparable extent as typically developing individuals.

5.3 Rationale of Study 2

Several imaging studies have reported that individuals with ASD have reduced or absent right FG activation during face processing tasks compared to typically developing individuals (6, 18, 314). However, recent imaging studies have reported that right FG activation is related to attention to the eyes region of the face in ASD (315) and comparable to typically developing controls when individuals with ASD attended to emotionally neutral faces (9). Therefore, Study 2 investigated if this high functioning group of young men with ASD [previously shown to have reduced right FG activation during the attribution of emotion in the EM task in Study 1] would have comparable right FG activation to typically developing individuals in a paradigm that required them to attend to the eyes region of the face, or if this group of young men would continue to have reduced right FG activation despite attending to the eyes region of neutral facial expressions. The later would provide evidence that individuals with ASD use an atypical perceptual strategy to process face percepts, despite attention to the eyes region, and suggest that atypical face processing strategies underlie the reduced expertise and right FG activation during the attribution of emotion from static facial expressions in these individuals with ASD.

5.4 Hypothesis of Study 2

- Individuals with ASD, who had reduced right FG activation during the EAP in the previous study, would have comparable right FG activation to the typically developing control group in a task that required them to attend to the eyes region of the face if right FG activation is associated to attention to the eyes region of the face.
- However, if right FG activation was related to reduced expertise in the perceptual processing of facial expressions or a predisposition toward atypical processing, then right FG activation would remain reduced in these individuals with ASD despite attention to the eyes region of the face.

5.5 Methodology Specific to Study 2

To address the aims of the study, 16 individuals with ASD and 10 typically developing individuals were recruited, as previously described. The GAP, which required attention to the eyes region in order to attribute the direction of gaze from stimuli, was presented to the same individuals as in Study 1. The GAP consisted of emotionally neutral faces and did not require attribution of emotion from facial expressions. Each stimulus consisted of a single static neutral face without linguistic labels, thus addressing this confound present in the EAP.

Participants performed the GAP while fMRI data was acquired on a 3 Tesla GE scanner. Accuracy and response time were measured as an indication of attention to the eyes region of the face during performance of the paradigm. All individuals had usable fMRI data collected during the GAP and were included in the WBA and ROI analysis. WBA was undertaken to investigate differential qualitative brain activation patterns in the right FG within and between groups and determine if individuals with

ASD activated the right FG during the implicit processing of face stimuli. Right FG ROI analysis was undertaken to determine if there were quantitative differences in right FG activation between the ASD and typically developing individuals while implicitly processing the neutral faces presented during the GAP.

5.6 Results of Study 2

5.6.1 Behavioural Measure Results

16 males with high functioning ASD diagnosed using DSM-IV (25) and 10 male control subjects were recruited. All high functioning individuals with a clinical diagnosis of ASD fulfilled the ADOS-G (21) criteria for the broader ASD, and those with a clinical diagnosis of autism also fulfilled criteria for autism using the ADI-R (20). The high functioning ASD group consisted of eight individuals with autism and eight individuals with AS. Brain scans from all recruited individuals were analysed.

5.6.2 Demographic and Neuropsychological Results

The ethnicity of the ASD group was eleven Caucasian, three Asian and two Hispanic individuals and the ethnicity of the control group was six Caucasian, two Asian, and two Hispanic individuals. The ASD and control groups were both of high socio-economic status. Within the ASD group two individuals were receiving methylphenidate, three were receiving serotonin reuptake inhibitors, and one was receiving both of these medications.

Sixteen males with ASD, eight with HFA and eight with AS (mean age = 13.8, SD +/- 2.8, range = 9-18 yrs) and ten male control subjects (mean age = 14.5, SD +/- 2.8, range = 10-18 yrs) were recruited. Independent sample *t*-tests showed no significant difference in age [$t(24) = -0.655$, $p < 0.519$] between groups.

Neuropsychological assessment showed that the ASD group [FSIQ = 112, SD +/- 14.9; VIQ = 103, SD +/- 19.8; PIQ = 120, SD +/- 11.5] and the control group [FSIQ = 116; SD +/-10.4; VIQ = 116; SD +/- 12.9; PIQ = 113; SD +/- 7.5] both had average to above average cognitive function. Independent sample *t*-tests showed no significant difference in intelligence [FSIQ: $t(24) = -0.868$, $p < 0.394$; VIQ: $t(24) = -1.883$, $p < 0.072$; PIQ: $t(24) = 1.69$, $p < 0.103$] between the two groups. Age and intelligence were not correlated with accuracy or response time.

There was no significant difference in accuracy [$t(24) = -0.486$, $p < 0.631$; ASD mean = 81%; SD +/- 14%; control mean = 84%, SD +/-15%] or response time [$t(24) = 0.374$, $p < 0.712$; ASD mean = 907 msec, SD +/- 184 msec; control mean = 883 msec, SD +/- 101 msec] between the ASD and typically developing groups during the attribution of gaze direction in the GAP. All subjects were right-handed [ASD = 90.4, SD +/- 9.6; control = 86.1, SD +/- 13.7] as determined by the EHI.

5.6.3 Whole Brain Analysis Results

Table 5-1 Whole Brain Analysis Gaze Attribution Paradigm

Within Group Brain Regions Control Group	P value	Number of Voxels	*z* score	Peak Talairach Coordinates
Left superior occipital gyrus BA 19	0.002	97	4.58	-30 -82 23
Right inferior occipital gyrus BA 18	0.000	1723	4.55	30 -90 -6
Right FG BA 37	0.000	196	4.40	42 -68 -7
Left FG BA 37	0.000	657	4.31	-42 -49 -16
Right middle frontal gyrus BA 9	0.000	393	4.16	53 15 25
Left thalamus-ventral lateral nucleus	0.000	89	3.79	-10 -13 3
ASD Group				
Right FG BA 19	0.000	859	5.01	38 -69 -13
Left superior parietal lobule BA 7	0.000	243	4.23	-32 -58 51
Left middle occipital gyrus BA 19	0.000	100	3.82	-34 -81 17
Right inferior parietal lobule BA 7	0.000	216	3.80	32 -56 43
Left middle occipital gyrus BA 19	0.000	163	3.74	-43 73 9
Left inferior frontal gyrus BA 9	0.000	87	3.21	-46 7 25
Between Group Brain Regions ASD – Controls Group				
Left middle frontal gyrus BA 8	0.000	219	3.59	-26 22 43
Right middle frontal gyrus BA 9	0.007	100	3.46	34 27 26
Right cuneus BA 19	0.003	123	3.39	16 -74 31
Right middle temporal gyrus BA 21	0.006	108	3.26	55 -24 -6

Left precuneus BA 7	0.001	156	3.16	-24 50 48
Right anterior cingulate BA 32	0.005	114	2.75	4 23 -8
Left anterior cingulate BA 32	0.000	209	2.68	-6 43 13
Controls - ASD Group				
Right lentiform nucleus - putamen	0.000	223	3.44	24 8 5
Right cuneus BA 18	0.000	254	3.42	10 -71 18
Right precentral gyrus BA 4	0.004	117	3.40	40 -13 41
Right cerebellum/ FG BA 19	0.000	314	3.07	24 -65 -17
Left precentral gyrus BA 4	0.000	360	3.00	-55 -12 28
Left lentiform nucleus - putamen	0.000	438	2.97	-29 -14 -3
Right superior temporal gyrus BA 22	0.006	108	2.94	46 -57 16
Right medial frontal gyrus BA 6	0.000	325	2.87	8 1 53
Left superior frontal gyrus BA 10	0.003	132	2.82	-36 50 21
Right pre-central gyrus BA 4	0.005	111	2.73	57 -4 21
Left superior temporal gyrus BA 22	0.008	97	2.70	-51 2 4
Right posterior cingulate	0.005	110	2.59	10 -44 6

Table 5-1 shows the significant clusters of activation (height threshold $p < 0.05$ and extent threshold $p < 0.05$ uncorrected for multiple comparisons) within and between group for emotionally neutral – scrambled faces in the Gaze Attribution Paradigm [Brodmann's Areas (BA)].

Within group analysis of the ASD group revealed significantly greater right FG activation (BA 19) for emotionally neutral faces - scrambled faces in the GAP. There also were smaller clusters of activation in the left superior parietal lobule (BA 7), left middle occipital gyrus (BA 19), right inferior parietal lobule (BA 7) and left inferior frontal gyrus (BA 9) (Figure 5-1).

Figure 5-1 ASD Group Whole Brain Activation for Gaze Attribution Paradigm

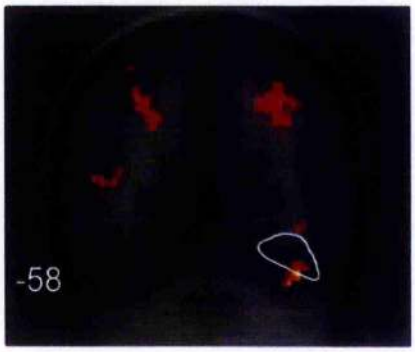


Figure 5-1 shows WBA significant right FG ROI activation during attribution of gaze from emotionally neutral faces - scrambled faces in the ASD group in the Gaze Attribution Paradigm.

Within group analysis of the control group also revealed a cluster of significantly greater activation in the right FG (BA 37) (for emotionally neutral faces than scrambled faces) in the GAP. Additional clusters of activation were observed in the left superior occipital gyrus (BA 19), right inferior occipital gyrus (BA 18), left FG (BA 37), right middle frontal gyrus (BA 9) and left thalamus in the control group (Figure 5-2).

Figure 5-2 Control Group Whole Brain Activation for Gaze Attribution Paradigm

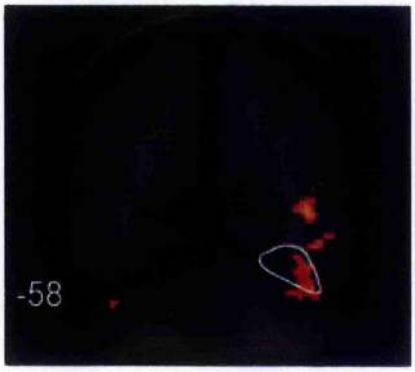


Figure 5-2 shows significant right FG ROI activation during attribution of gaze from emotionally neutral faces - scrambled faces in the control group in the Gaze Attribution Paradigm.

The between group analysis for emotionally neutral faces - scrambled faces in the GAP showed that the control group had greater activation in the right FG (BA 19) than the ASD group. The control group also had greater activation than the ASD group in the right and left putamen, right cuneus (BA 18), right and left precentral gyrus (BA 4), right cerebellum, right and left STG (BA 22), right medial frontal gyrus (BA 6), left superior frontal gyrus (BA 10) and posterior cingulate gyrus.

Figure 5-3 Region of Interest Activation in the Gaze Attribution Paradigm

Figure 5-3 shows greater right FG ROI activation in the control-ASD group contrast (green activation) but no areas of greater right fusiform ROI average activation in the ASD-control group contrast (red activation) during the attribution of gaze from neutral faces than scrambled faces in the Gaze Attribution Paradigm.

The ASD group had greater activation than controls in the left middle frontal gyrus (BA 8), right middle frontal gyrus (BA 9), right cuneus (BA 19), right middle temporal gyrus (BA 21), left precuneus (BA 7) and bilateral anterior cingulate (Figure 5-3).

5.6.4 Region of Interest Analyses Results

Figure 5-4 Right Fusiform Gyrus Activation in the Gaze Attribution Paradigm

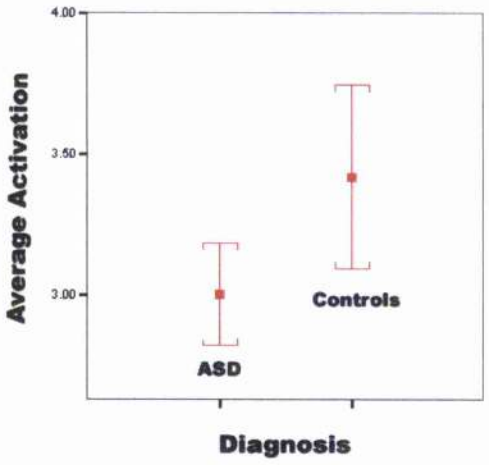


Figure 5-4 shows significantly greater average activation in the right FG in the control group than the ASD group in the Gaze Attribution Paradigm.

Between group comparison of average voxel activation showed that controls had a significantly greater average right FG activation than the ASD group for emotionally neutral faces - scrambled faces in the GAP [$U = 40$, $p < 0.035$; ASD mean = 3.00, SD +/- 0.36; control mean = 3.44, SD +/- 0.562] (Figure

5-4). There were no significant group differences in average left FG activation for emotionally neutral faces - scrambled faces in the GAP.

5.7 Data Interpretation 2

Both the ASD and the control groups had comparable accuracy and response time, indicating comparable attention to the eyes region of the emotionally neutral faces during the GAP. Differing performance potentially confounds the interpretation of brain activation (294), hence, comparable performance on the GAP facilitated the comparison of brain activation between the ASD and typically developing group in this study. WBA was employed to determine if individuals with ASD exhibited differences in functional activation of the right FG while attending to the eyes region of the face to attribute gaze direction from static neutral faces. Within group WBA revealed that both the ASD and control group activated the right FG when attending to the eyes region of these emotionally neutral faces. Between groups WBA revealed that the ASD group had less activation in the right FG during the GAP than the control group. The ASD group showed less bilateral activation in the putamen, precentral gyri and superior temporal gyri. Compared to typically developing individuals, individuals with ASD showed less unilateral activation in the right cerebellum, right medial frontal gyrus, right posterior cingulate gyrus, left superior frontal gyrus and right cuneus in the GAP. The ASD group appeared to be more dependent on regions outside the right FG, including bilateral middle frontal gyri, anterior cingulate and right middle temporal gyrus, and unilateral left precuneus and right cuneus involved in object location, compared to typically developing individuals in the GAP. These findings provide evidence that these high functioning individuals with ASD, even when attending to the eyes region of faces to attribute the direction of gaze, do not exhibit the typical neurofunctional response to emotionally neutral faces.

Follow-up ROI analyses confirmed that the relative reduction in right FG activation persisted in this group of individuals with ASD, despite attention to the eyes region of the face, compared to the age- and sex-matched typically developing control group. This is in contrast to the findings of a recent fMRI study by Hadjikhani and colleagues that found comparable right FG activation to typically developing individuals when individuals with ASD attended to a cross placed between the eyes in neutral faces stimuli (9). The reduced right FG despite attention to the eyes region may reflect that the individuals with ASD in Study 2 were younger and, therefore, neurodevelopmentally less expert than the older individuals in the study by Hadjikhani and colleagues (9). Another possible explanation for the difference between this and the presented study relates to aetiological heterogeneity. ASD is aetiologically heterogeneous (317), therefore, not all individuals with ASD would be expected to have face processing deficits as an explanation for their SCI. Differences between studies would be expected as a consequence of aetiological heterogeneity for the SCI in ASD. The persistent reduced right FG activation during the GAP may also reflect that the individuals with ASD had perceptual processing deficits already identified by their poor performance on the EM task, which had greater perceptual processing demands than the EL task, in Study 1.

Another study by Dalton and colleagues (203) found that individuals with ASD had reduced right FG activation compared to typically developing individuals. This study found that gaze fixation on the eyes

regions of the face was positively related to right FG activation in the ASD group, but not in the typically developing group. Gaze aversion was associated with reduced amygdala activation in the ASD group and the subjects with autism gazed less at the eyes region of facial stimuli. In this study, these aberrant patterns of facial processing strongly predicted: behavioural performance when subjects were asked to judge whether a face is neutral or emotional; and, the duration of gaze on the eye region of a face strongly predicted the magnitude of activation in the FG. The social impairment domain of the ADI-R was controversially used as a measure of social impairment severity, and the amygdala activation shown to correlate with the severity of the ADI-R social impairment domain, which is actually a categorical variable and so not strictly speaking suitable for correlation analysis.

As eye-tracking technology was unavailable in the scanner at the time of this study and so actual attention to the eyes region of the face was not measured, so reduced right FG may represent reduced attention to this region in individuals with ASD. Activation of the FFA has been found to be dependent on the level of attention paid to the face stimuli, and FFA activity reduced when the face stimuli is not the focus of the participant's attention (238). However, reduced right FG secondary to reduced attention to the eyes region of the face seemed an unlikely explanation for the activation differences as the paradigm presentation was 2 seconds and average response times were similar in both groups. Differences in attention to the whole face/ configural processing demands between the EM and EL tasks in the EAP and GAP could explain the differences in brain activation in these and other recent studies,

Alternative explanations also need to be considered. The GAP required attention to the eyes regions of the face as this was related to right FG activation in previous studies; however, the attribution of gaze direction can be successfully achieved using feature-base perceptual processing strategies (255). Therefore, in the GAP study, either or both of the groups could have attributed the direction of gaze from attending to the eyes region of the face, without the implicit perceptual processing of the emotionally neutral face stimulus. Typically developing individuals have an innate drive toward the implicit processing of faces (189), whereas individuals with ASD may attend to the aspects of the face, such as the eyes region in the GAP task and not implicitly process the entire face. There is evidence that the processing of gaze direction is carried out in a feature-based manner using local features around the eyes and does not require configural processing (255). A predisposition toward this and other atypical face processing strategies in the ASD group, may have led to the finding of reduced right FG activation despite attention to the eyes region of the face in the GAP. Further investigation is needed to determine if configural processing demands or gaze fixation on the eyes region of the face modulates right FG activation and accounts for the group differences in right FG activation seen in these high functioning young men with ASD in this study.

Reduced right FG activation in this group of individuals with ASD, during a task that does not require the attribution of emotion from static facial expressions, provides evidence for an atypical face processing strategy in individuals with ASD rather than a specific processing deficit in the attribution of emotion from static facial expressions. However, an atypical feature-based face processing strategy as a

result of a deficit in configural processing would also result in a deficit in the attribution of emotion from static facial expressions in tasks that required the configural processing of facial expressions.

The persistent right FG hypo-activation in both this face processing study and the EM task in the facial expression processing study (296) would support a relatively reduced specialisation of the right FG for configural processing of faces in this group of high functioning individuals with ASD (7). However, the comparable right FG activation in the EL task in the previous emotion attribution study suggests that there is sufficient right FG specialisation in these individuals with ASD for the processing of single facial expressions. The reduced right FG activation when individuals with ASD attribute emotion from facial expression in the EM task and attend to the eyes region of faces in the GAP may reflect a relative reduction in right FG specialisation in individuals with ASD and/ or a reduced attention to the whole face.

Developmental studies are necessary determine the mechanism of specialisation of the right FG in individuals with ASD (228) and the mechanism of right FG specialisation for faces remains contentious. Some argue that the right FG is innately specialised for the processing of faces (232), whereas others suggest that experience-dependent specialisation of the right FG occurs for faces and other percepts for which the individual develops expertise (187). The relatively reduced right FG activation seen in the EM task and the GAP may reflect relatively reduced innate or experience-dependant specialisation of the right FG in individuals with ASD. Individuals with ASD have a reduced predisposition to engage in social interaction (318) and faces have been suggested to be of less social salience for individuals with ASD (288). If specialisation of the right FG in these young men with ASD is relatively reduced then this is consistent both with reduced experience-dependent right FG specialisation (7) and reduced innate specialisation of the right FG in ASD (232). The recruitment of the same individuals across studies provides evidence for the use of an atypical processing strategy across paradigms. The use of an atypical processing strategy would explain the comparable right FG findings in the EL task of the EAP and account for the findings in this study and the EM task in the previous categorical study. .

5.8 Key Findings of Study 2

Contrary to recent studies (9, 203), reduced right FG activation continued despite attention to the eyes region of the face in a well-characterised group of individuals with ASD, who previously had demonstrated reduced right FG activation while attributing emotion from facial expressions in the EAP in Study 1 (296). These individuals with ASD had reduced right FG activation despite performing a task that emphasised attention to the eyes region of emotionally neutral faces. Reduced right FG activation may still represent reduced attention to the eyes region of the face. However, it is more likely related to reduced configural processing of the whole face in individuals with ASD either secondary to a predisposition toward an atypical perceptual strategy or reliance on an atypical perceptual compensatory strategy because of relatively reduced configural processing capacity in the ASD group.

The use of a compensatory atypical face processing strategy to address the reduced capacity to configurally process faces in ASD, offers a possible explanation for the preserved ability to perform the GAP despite reduced right FG in individuals with ASD. This would be in keeping with the task-

dependant findings in Study 1. Individuals with ASD may be less expert at the EM task because it had an inherently greater configural processing load, but as able to configurally process the lesser configural processing load presented in the EL task. Another possible explanations for the preserved ability to perform the GAP despite the reduced neural activity observed in the right FG in individuals with ASD, is a predisposition toward an atypical face processing strategy whilst having the capacity to configurally process faces, as proposed in the enhanced local perceptual precedence hypothesis. This would also be in keeping with the task-dependant findings during the EAP in Study 1, and consistent with configural processing in attribution of emotion from one facial expression in the EL task, and feature-based processing and matching of the characteristics from the three facial expressions in the EM task.

Another possible explanation for the disparity with other studies is aetiological heterogeneity (11). The high functioning individuals with ASD, who participated in this study, were known to have face processing deficits. However, not all individuals with ASD have face processing deficits, and so would not be expected to have reduced right FG activation. This aetiological heterogeneity in ASD offers another possible explanation for the divergent right FG findings in ASD (203, 319).

5.9 Methodological Considerations of Study 2

The following methodological issues with respect to subject recruitment, behavioural measure, paradigm design and procedure, and whole brain analysis need to be taken into account when considering the findings of this study.

5.9.1 Subject Recruitment

The participation of these young men with ASD in the GAP and the EAP permits comparison of neural activation in the same group across these different paradigms. Use of the same group of young men with ASD, known to have deficits in the attribution of emotion, meant that it was possible to address some of the limitations in Study 1 in the same participants and investigate if these young men actually have face processing deficits when attributing gaze direction from static facial expressions.

5.9.2 Behavioural Measures

Future studies with larger AS and HFA groups should be undertaken to determine if HFA and AS are functionally different when they attribute emotion from facial expressions. Previous structural imaging studies showed significant grey matter differences between AS and autism (320); however, other studies suggest that HFA and AS exist on a continuum of 'affectedness'.

The continued use of categorical measures prevents investigation of the relationship between SCI, performance during the attribution of emotion from static facial expressions. Future fMRI studies should investigate the relationship between the SCI seen in ASD, and performance in attribution of emotion from static facial expressions tasks; and using eye-tracking technologies determine the relationship between visual processing of the face, emotion attribution deficits, and right FG activation. Modification of behavioural variables such as gaze fixation provides leverage to address whether the right FG findings are as a result of abnormal right FG development, atypical visual strategies or reduced attention to the eyes region of the face in ASD.

5.9.3 Paradigm Design and Procedure

For both the ASD and control groups, the performance variables were comparable in the GAP, hence, the neural correlates of the GAP could be directly compared between groups, addressing this limitation in Study 1. However, both the ASD and the control groups could have attributed the direction of gaze in the GAP without implicitly processing the face, and as the GAP did not necessitate the use of configural processing, it had the same potential limitation as the EM task in Study 1.

Gathering behavioural data that explicitly confirms that a particular cognitive strategy has been undertaken can be problematic. Fixation and registration of a response to a facile task can be used to infer implicit task performance. For example, in the GAP implicit face processing was assumed while the participants explicitly determined the direction of gaze. However, implicit face processing may not have occurred in the ASD group, the control group or, indeed, may not have occurred in either group. Future studies should objectively measure visual fixations and determine the actual visual strategies used by each group. Objective measurement of the perceptual strategies used by high functioning individuals with ASD will be facilitated by the advent of eye-tracking capabilities and incorporation during fMRI. In particular eye-tracking technology should be use to determine individuals with ASD patterns of attention to the eyes and the whole face during experiments.

5.9.4 Whole Brain Analysis

In contrast to Study 1, WBA was undertaken in Study 2 prior to ROI analysis. Analyzing brain-imaging data involves creating SPM for a brain dataset. SPM are brain images made up of single or multiple (combined) subjects, where each voxel has an associated statistic. Thus, SPM can be used to test hypotheses about the function of a given brain region by examining the activity on the voxel level with an associated statistic. The researcher examines the brain volume to determine which brain regions are active during an experimental task for an experimental group. Despite the popularity of this approach, SPM does not directly explore the functional relationships between different brain regions, as SPM treats each voxel as an isolated entity (46). As neurons in the brain have many connections to many other neurons and form a neural network of connected activity, researchers have become interested in connectivity analysis in ASD. Future connectivity studies are required to examine neural circuit architecture in ASD.

There are other limitations and practical problems with voxel-based approaches like WBA. One statistical problem is the large number of comparisons within a small spatial region, which reduces statistical power. When correcting for these multiple comparisons many degrees of freedom are required. As many fMRI studies have small sample size, the need to reduce multiple comparisons has led to an approach where voxels are combined into manually defined anatomical regions for each subject. In this study, statistically active voxel intensities were averaged over an anatomically defined ROI for each subject. This approach provides for a more powerful statistical test given the same number of subjects than the voxel-based approach. Another advantage of this technique over the voxel-based approach is that by collapsing data for anatomically related voxels into one measurement the relationships between user-defined regions, rather than image-defined voxels, are quantifiable.

In this study, within group WBA was undertaken to determine if typically developing individuals activated the right FG in the GAP. Brain activation patterns in typically developing individuals had not previously been studied using the GAP. Within group WBA was also undertaken to determine if the right FG was activated in the ASD group and between groups analysis undertaken to identify those voxels that are differentially activated in the ASD group verses the control group. This qualitative approach supported that the ASD groups activated the right FG but less so than the control group.

Significant differences between groups can be a result of either significant activation in the experimental group and, therefore, of interest, or as a result of significant deactivation in the control group, which confounds interpretation of the between group activations. In this study, deactivation in the control group was identified to ensure that activation clusters represented activation in the experimental group and were not a result of the deactivation in the control group. Between groups WBA comparisons in this study represent differential activations between groups, and corroborated the findings of the quantitative ROI analysis.

The location of the activated brain regions were determined in this study, as they are in most other studies, using the Co-Planar Stereotaxic Atlas of the Human Brain (44). This atlas was produced from photographs of sections of the brain of a 60-year-old woman. Therefore, the brain used to produce this atlas is not representative of male brains of any age, or of female brains of most ages. Furthermore, despite functionally significant anatomical differences between the right and left hemispheres, photographs of the left-brain were reversed, and used to represent the right brain. Therefore, averaged functional activation images projected on to this atlas do not accurately represent the actual location of activation in most brains. In this thesis, a database of previously published imaging results, called 'Tal Daemon' (321), was also used to compare the brain regions reported across studies for Tal co-ordinates.

5.10 Conclusions and Implications of Study 2

The same individuals with ASD as undertook the EAP undertook the GAP, which involved explicit attention to, and determination of, gaze direction and by inference the implicit processing of neutral valence faces. Previous studies have proposed that reduced right FG activation is a consequence of reduced attention to the eyes region of the face in individuals with ASD and have suggested that right FG is not a crucial component in the face processing deficits seen in ASD (9, 203). Therefore, the hypothesis was that the individuals with ASD, who had reduced right FG activation during a face processing task in Study 1, would have comparable right FG activation to a typically developing control group. Specifically, in a task that required them to attend to the eyes region of emotionally neutral faces, if right FG activation was associated to attention to the eyes region of the face. However, if right FG activation was related to reduced expertise in the perceptual processing of facial expressions or a predisposition toward atypical processing, then right FG activation would be reduced despite attention to the eyes region of the face. Reduced right FG activation was observed in this well-characterised group of individuals with ASD, who previously had demonstrated reduced right FG activation in the EM task of the EAP (296), despite attending to the eyes region of emotionally neutral faces. Therefore, the finding of this study support that the right FG activation is related to reduced expertise in the perceptual

processing of facial expressions or a predisposition toward atypical processing. High functioning individuals with ASD have been reported to be predisposed to feature-based processing. Potentially, the GAP could have successfully completed the GAP using feature-based component processing of the eyes region of the face. Therefore, this study did not definitively determine if individuals with ASD are able to configurally process faces when necessary for the successful completion of the task.

Further studies are needed to address the limitations of this study. Dimensionalisation of autism symptomatology rather than continued use of categorical diagnosis is necessary to allow the relationship between SCI, face processing and neural activation during the attribution of emotion from facial expressions to be determined. More naturalistic tasks that directly related to SCI, and require continuous attention to execute explicit configural face processing tasks are required. Experiments need to integrate the different levels of explanation for SCI and investigate the relationships between right FG activation, expertise in the attribution of emotion from facial expressions and SCI to develop an actiologically valid explanatory model for SCI.

Chapter 6 Synthesis of the Categorical Studies

6.1 Discussion of the Categorical Studies

The categorical studies presented were designed to determine the neural associations of SCI in ROI known to be involved in the attribution of emotion from static facial expressions and explore the cognitive and functional levels of explanation for SCI in ASD. Many cognitive constructs have been proposed as the primary cognitive deficit in ASD including TOM, EF and CC. Of these CC, which is a style of perceptual processing, best fulfils criteria as a primary cognitive deficit in ASD as it, potentially, explains the aptitudes, as well as the deficits seen in individuals with autism. Researchers have proposed that perceptual deficits in face processing play a causal role in the SCI seen in ASD (11). Several cognitive models of face processing, which related to CC, have been proposed including the featural/ holistic, component/ configural and enhanced local perceptual precedence models. These cognitive models have different inherent assumptions when applied to the perceptual deficits in ASD. Featural/ holistic and component/ configural models propose the atypical use of feature-based perceptual processing in ASD as a compensatory perceptual processing mechanism related to a reduced capacity to configurally/ holistically process percepts. Whereas, the enhanced local perceptual precedence model proposes a predisposition toward local processing despite having the capacity to configurally process percepts. Indeed, children with autism, have been found to be better at recognizing isolated facial features, and partially obscured faces, than typical developing children (212, 214). Individuals with autism also recognise inverted faces better than typical developing children (212, 213) and spend equal time looking at inverted faces compared with upright faces (215). Despite numerous research studies predominantly of facial recognition, it remains unclear if there is a deficit in configural processing in ASD or if individuals have an enhanced local perceptual precedence, and despite having the capacity to configurally process using feature-based approaches. These models of face processing have not been investigated in facial expression processing in ASD, but this too has been reported to require configural processing, and this is of potential interest when considering the underlying aetiology of the SCI in ASD. Indeed another plausible explanation for SCI in ASD is reduced expertise in the attribution of emotion from facial expressions. However, despite being acknowledged as a potential explanation for the SCI in autism (1) there has actually been little previous research in the attribution of emotion from facial expressions in ASD (11).

Social communication involves the perceptual, emotion and cognitive processing of the facial gestures of other people to attribute the emotion from facial expressions (2). Emotion attribution from static facial expressions has been shown to activate the FG, amygdala and prefrontal cortex in typically developing individuals associated with perceptual, emotion and cognitive processing of facial expressions respectively (12). Therefore, emotion attribution from static facial expression activates those ROI in typically developing individuals, which are frequently argued in the literature to be aberrant in ASD. The three ROI are, potentially, informative when investigating the underlying aetiology of SCI and were investigated during the attribution of emotion attribution from static and dynamic facial expressions in the categorical and dimensional studies respectively.

Expertise in the attribution of emotion from facial expressions and face processing has been related to experience with faces in ASD (240, 249). Reduced expertise in the attribution of emotion from facial expressions has been associated with SCI (275) and the use of atypical visual processing strategies in autism (18). Individuals with ASD provide an opportunity to investigate the neural correlates of emotion attribution from facial expressions in individuals who, potentially, have accrued less experience with faces and facial expressions. Several studies have reported that autistic children exhibit impairments in the interpretation of facial emotions from static images compared to typically developing children (212, 214, 252). Although emotion attribution from facial expressions was acknowledged in a recent review article (1) to have great face validity as an explanation for the SCI in ASD, no studies have looked at the attribution of emotion from facial expressions in high functioning individuals with ASD and investigated the role of ROI involved in typically developing individuals.

The categorical studies focused on paradigms that isolate emotion attribution from static facial expressions as the CCI to determine if emotion attribution deficits underlie the SCI the core deficit in ASD (1, 2). The categorical studies hypothesised that individuals with ASD would demonstrate reduced expertise in the attribution of emotion from static facial expressions associated with atypical neural activation in ROI known to be activated in typically developing individuals. In keeping with this hypothesis, the categorical studies found that individuals with ASD are less expert in the attribution of emotion from static facial expressions associated with reduced right FG activation; however, this was task-dependant. In the EAP, individuals with ASD had comparable expertise and ROI activation in the amygdala, prefrontal and FG ROI during the EL task, which had linguistic facilitation. The EL task findings of the categorical studies support the individuals with ASD have the capacity to attribute emotion from static facial expressions. However, this is task-dependant, and individuals with ASD had reduced expertise and right FG activation in the EM task, which had a greater perceptual/ emotion attribution load than the EL task. The same individuals with ASD had reduced right FG activation while attributing the direction of gaze from neutral static face percepts in the GAP, despite attention to the eyes region on the face. Therefore, the categorical studies provided evidence for comparable cognitive and emotion processing and task-dependant atypical perceptual processing during the attribution of emotion from static facial expressions in individuals with ASD. The categorical studies also provide evidence that reduced right FG activation is not related to attention to the eyes *per se* in the ASD group, although reduced right FG may be related to reduced attention/ configural processing of the whole face. Indeed, attention to faces and configural processing of faces might be overlapping or dependent constructs. If attention to the face is important in the activation of the right FG, then inattention to the face would be expected to result in reduced right FG activation, whether the right FG had undergone innate or experience-dependant specialisation for face processing or not.

Differences in the neural correlates of emotion attribution from static facial expressions did relate to diagnosis in the categorical studies. Individuals with ASD, who are hypo-sociable, were less expert in the attribution of emotion from static facial expressions associated with reduced right FG activation in comparison to typically developing individuals in the EM task. There is a longstanding debate, as to whether, expertise for face processing is a result of innate specialisation or experience-dependant

specialisation of the right FG (230-232). In the experience-dependant FG specialisation model there has been an eagerness to relate the lack of perceptual expertise in ASD to their hypo-sociability and reduced experience with face percepts to reduce expertise in the processing of faces. However, these cognitive models investigating the development of expertise in face processing have largely been based on research undertaken in the sphere of facial identity recognition. In facial identity recognition studies, increased right FG activation has been associated with increased expertise in the identification of individual faces, which requires perceptual and facial memory processing. Although the right FG has recently been associated with the attribution of emotion from facial expressions, how right FG activation relates to expertise in facial expression processing remains unclear.

Studies of experience-dependent specialisation of the right FG suggest that specialisation occurs for all exemplars for which the individual has accumulated the experience to develop expertise. Experience requires the individual to be 'interested' and process many exemplars. Previous fMRI studies comparing face to Digimon character processing in a young man with an interest in Digimon did not control for attention to the percepts. The individual with autism studied was more interested in the Digimon character percepts, which activated the right FG in the same brain region as faces in typically developing individuals. This demonstrates the interpretation difficulty when attention is not control in this area of research. Interest results in attention, which has an intensity as well as a time, construct and attentional patterns are related to perceptual strategies. Hence, it is difficult to disentangle interest, attention and perceptual processing strategies such as configural processing in ASD, without the use of eye-tracking technology. As individuals with ASD are assumed not to have accrued the same experience with faces, reduced experience-dependant specialisation of the right FG has been proposed to explain the SCI in these high functioning individuals with ASD. However, others contend that the right FG is innately specialised for face processing and that reduced right FG activation in ASD is related to reduced attention to the face during fMRI paradigms (232, 322). This has been borne out to some extent in recent eye-tracking studies, which have found that right FG activation was related to attention to the face in groups of individuals with ASD (203). However, parametric studies looking at right FG activation with increasing attention to the face in single individuals with autism are necessary to determine the relationship between activation and attention in ASD.

Previous studies that reported reduced right FG activation in ASD proposed this as conducive with reduced experience-dependent specialisation of the right FG (240); however, the alternate theory reduced innate right FG specialisation has not been discounted. The categorical studies despite reduced right FG specialisation in the EM task and the GAP, found comparable performance in the attribution of emotion in the EL task in Study 1 in this population of high functioning young men. Therefore, the categorical studies do not support a lack of right FG specialisation explanation in these high functioning young men with ASD. The behavioural and functional findings of the EL task suggests that individuals with ASD have either innate specialisation of the right FG or get sufficient experience of facial percepts to develop experience-dependant right FG specialisation. The experimental designs used in the EM task in Study 1 and the GAT in Study 2 do not allow us to determine between these FG specialisation theories or allow us to determine if the degree of specialisation is comparable to typically developing. Right FG

specialisation, by virtue of either mechanism, is comparable between groups in the EL task. A relative reduction in specialisation in the ASD group, reduced attention to the whole face, and use of feature-based perceptual processing in ASD would explain the reduce right FG activation in the EM task in the EAP and the GAP in the categorical studies. A predisposition/ precedence toward feature-based perceptual processing in ASD despite having the ability to configurally process faces or a compensatory strategy in tasks with greater perceptual processing demands that outstrip the individuals configural processing capacity would explain the reduce right FG activation in the EM task in the EAP and the GAP in the categorical studies.

Other possible explanations for the findings in the categorical studies include paradigm design, implicit/ explicit face processing, language facilitation and enhanced local perceptual precedence and are explored in the following sub-sections. Consideration of the cognitive constructs isolated by the EL and EM tasks in the EAP and the GAP provided evidence that reduced right FG was associated with face and face processing tasks that could be successfully completed without configural processing through the use of atypical perceptual processing strategies. So one possible explanation relates to the use of tasks that potentially do not solely depend on configural processing. Our limited understanding of configural processing presents another challenge in terms of remediating our experimental design and interpreting the resulting neural activation during further face processing paradigms. Configural processing has recently been associated with visual fixation (323) and spatial frequency patterns (324). These parameters potentially provide a bridge between behaviour and neural activation patterns that can be used to better understand the neural activation patterns associated with configural processing.

Hypo-activation of the right FG in individuals with ASD may also be related to the implicit or explicit nature of the task. The categorical studies provide evidence for configural processing in the EL task, which had explicit instructions and hypo-activation of the right FG in the EM task of the EAP and GAP, in which face/ facial expression processing was an implicit aspect of the task. Previous studies have reported redressed neural activation in individuals with ASD when implicit face processing tasks are made explicit (325). Language facilitation in facial identity tasks in individuals with AS has also been previously reported to improve performance in individuals with ASD (164). The language facilitation in the EL task may explain the comparable right FG activation in the ASD group. However, the fact that cognitive models of face processing and research on the development of expertise in face processing have largely been undertaken in the sphere of facial identity recognition limits our capacity to interpret this report. In facial identity recognition studies, increased right FG activation has been associated with increased expertise in the identification of individual faces, rather than increased expertise in facial expressions processing in ASD and the configural processing demands may or may not be similar.

Previous studies have also proposed enhanced local perceptual precedence in ASD despite the capacity for comparable configural processing. The categorical studies support that these high functioning individuals with ASD do have the capacity to configurally process percepts and are supportive of the use of atypical perceptual processing strategies in ASD; however, investigating for evidence in support of enhance local perceptual precedence was beyond the scope of the categorical studies presented.

6.2 Conclusions of Categorical Studies

Hence, the hypothesis that reduced expertise during the attribution of emotion from static facial expressions was related to reduced right FG specialisation for the perceptual processing of faces in ASD, as previously reported in autism, was upheld. However, this atypical perceptual processing during the attribution of emotion from static facial expressions for the SCI in ASD was task-dependent. There were no prefrontal or amygdala activation abnormalities during emotion attribution from static facial expressions providing evidence that cognitive and emotion processing during the attribution of emotion from static facial expressions is not atypical in these high functioning individuals with ASD. The categorical studies support an association between SCI and atypical perceptual processing during the attribution of emotion from static facial expressions and provide evidence for no association with atypical cognitive or emotion processing in ASD. The same individuals with ASD still had reduced right FG activation while attributing the direction of gaze from neutral static face percepts in the GAP, despite attention to the eyes region on the face. This provides further evidence for atypical perceptual processing in ASD and suggests that reduced attention to the eyes *per se* does is not associated with reduced right FG activation in ASD, although attention to the whole face was not investigated.

Despite the task-dependant nature of the findings in these high functioning young men with ASD the categorical studies provide preliminary evidence to support atypical perceptual processing during the attribution of emotion from facial expressions. Atypical perceptual processing provides a potential cognitive level explanation and reduced right FG a potential functional level explanation for the SCI seen in ASD informing the development of a preliminary explanatory model for SCI in ASD. However, the relationship between SCI in ASD, emotion attribution form facial expressions and right FG activation could not be established from the categorical studies. To further inform the development of an explanatory model for SCI and determine if right FG specialisation for the configural processing of facial expressions offers an explanation for SCI seen in ASD the dimensional fMRI studies were undertaken.

6.3 Implications of Categorical Studies

Although the categorical studies supported an association between perceptual processing and right FG activation during the attribution of emotion in the EM task of the EAP and the GAP these paradigms may not have necessitated configural processing. The categorical studies found that high functioning individuals with ASD were able to attribute emotion from static facial expressions such as the facial expression in the photographs in the EL task of the EAP. Anecdotally, these individuals are less able to attribute emotion in actual social situations when confronted with dynamic facial expressions. The dimensional studies attempted to address the behavioural, cognitive and functional limitations of the categorical studies. The categorical studies used categorical measures of behaviour to diagnose ASD, and by inference identified individuals as having SCI for participation. The categorical studies then investigated the association between SCI in ASD, emotion attribution from static facial expressions and activation in hypothesis-driven ROI chosen *a priori*. The identification of atypical perceptual processing in individuals with ASD emphasised the need to quantify SCI and investigate for correlations between cognitive and functional levels of explanation to further explanatory models of ASD. In the categorical studies, individuals with HFA and AS, which have clear diagnostic inclusion criteria, were studied;

however, individuals who did not fulfil criteria for either of these diagnoses were excluded because of the lack of clear diagnostic criteria even although it was clinically evident that they had SCI impairment qualitatively similar to that seen in HFA and AS. Quantification of continuously distributed characteristics and the creation of a 'continuum of affectedness' offers the opportunity to include all individuals expressing varying degrees of SCI in aetiological research. The quantification of continuously distributed characteristics allows the relationships between variables to be explored and is a more powerful approach for aetiological study (326).

By implication, the categorical studies highlighted the need for a dimensional approach to SCI to establish the relationship between SCI, emotion attribution and ROI activation, and necessitated the development of a paradigm that required the configural processing of dynamic facial expressions for use in subsequent emotion attribution studies. The categorical studies informed the design of the DFEP for use in the dimensional studies dictating that: the paradigm should have no linguistic scaffolds; be controlled for visual processing load; and, require the configural processing of facial expressions. Therefore, the facial expressions in the DFEP were dynamic, more naturalistic and could only be successfully completed using configural analysis. The DFEP also required continuous attention to the whole face as the facial expression developed. Individuals with ASD have been reported to use feature-based processing supported by the ITG, in non-inverted and inverted facial expressions, as opposed to the typically developing individuals, who use configural processing supported in the right FG for non-inverted face percepts, but show an inversion effect and process inverted faces using feature-based processing supported by the ITG (327, 328). Therefore, an inverted dynamic facial expression condition was incorporated as a comparison condition to the non-inverted dynamic facial expressions in the DFEP.

The dimensional studies undertaken in Part III of this thesis determine the relationship between SCI measured as a dimension of behaviour, expertise in the attribution of emotion and activation in the FG and ITG ROI involved in the perceptual processing of faces during emotion attribution from non-inverted and inverted dynamic facial expressions.

PART III: DIMENSIONAL STUDIES

Chapter 7 Social Communication Impairment and Emotion Attribution from Dynamic Facial Expressions in Individuals with Social Communication Difficulties

7.1 Introduction to Dimensional Studies

The dimensional studies explore the relationship between behavioural, cognitive and functional levels of explanation for SCI. To explore this relationship autistic symptomatology was dimensionalised and the relationship between SCI, expertise in the attribution of emotion and activation in two ROI, the FG and ITG ROI, investigated during the attribution of emotion from dynamic facial expressions. These studies further investigate if reduced right FG specialisation for configural processing of face percepts and consequent reduced expertise in the attribution of emotion from facial expressions offers an explanation for SCI in high functioning young men with SCD. The dimensional studies presented in this thesis aimed to 'integrate' behaviour, cognitive and functional levels of explanation and develop an integrated aetiologically valid explanatory model for SCI in high functioning young men with SCD, the criteria for which are reviewed.

7.2 Model of Social Communication Impairment - Levels

Any explanatory model for SCI would ideally have an evolution, a developmental trajectory and facilitate an integrated behavioural, cognitive, functional and genetic explanation of SCI as seen in ASD (Figure 7-1).

Figure 7-1 Explanatory Model for Social Communication Impairment

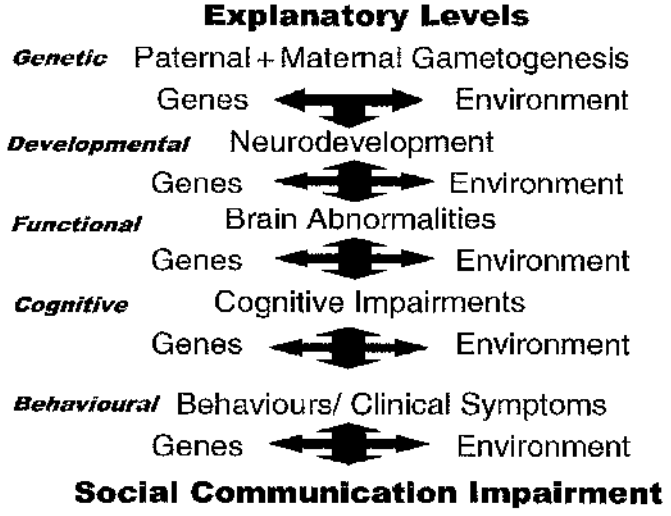


Figure 7-1 shows the levels of explanation that need to be integrated when developing an aetiologically valid explanatory model of social communication impairment.

An evolutionary valid construct would have an evolutionary trajectory in humans and other species, and in humans would have evolved under environmental and social selection pressures (329). The existence of an evolutionary trajectory for SCI would infer the aetiological validity of the construct and, potentially, the existence of homologous constructs across species. The rapid development of animal models in psychiatric genetics has, in part, occurred due to the realisation that there are homologous cognitive constructs in other species (330). The advent of animal models for homologous cognitive constructs has allowed the aetiological validity of the respective explanatory models to be investigated [e.g. mouse models have allowed the development of an explanatory model at the functional (5HT), cognitive (impulsivity) and behavioural (ADHD) level for hyperkinetic disorder (331)].

Developmentally valid constructs require to have a neurodevelopmental trajectory. The existence of a neurodevelopment trajectory not only infers the aetiological validity of the construct, but also allows comparison of 'actual' neurodevelopment with 'expected' neurodevelopment for chronological age. Developmental constructs facilitate identification of atypical neurodevelopment and the explanation of atypical development in terms of the deviation or delay of typical development. An understanding of atypical development in terms of typical development has been identified as a necessary prerequisite for aetiologically valid explanations in developmental disorders (332). The identification of a developmental construct as an explanation for SCI would add to the aetiological validity of the construct in an explanatory model.

An aetiologically valid behavioural construct ideally requires all observed behaviours within the behavioural domain to have a common underlying aetiology. The behavioural approach is based on overt, discernable behaviours that can be measured either qualitatively or quantitatively, and the aetiological validity of the behaviour investigated at the cognitive, functional and genetic level of enquiry. In clinical practice, disorders are described in terms of behaviour, which includes standardised measures of their cognitive aptitude or 'intelligence'. However, the terms 'behaviour' and 'cognitive' have distinct meanings in the explanatory model for SCI developed in this thesis. Behaviour refers to what the individual does without reference to how and cognitive is reserved for how the individual does the behaviour, a crucial distinction in the development of explanatory models for complex constructs like SCI.

To establish the aetiological validity of a cognitive construct requires investigation of the underlying cognitive processes by which the individual performs a particular behaviour. An individual may display the same behaviours or performance during a task, but be using a different cognitive strategy, which is not overtly discernible at the behaviour level. The term cognitive in the model refers to the underlying strategies by which any particular task can be completed and recognises that, in some tasks, a number of cognitive strategies can be successfully employed. Different cognitive strategies or approaches can be obvious through measurement of performance variables such as accuracy and response time during the task. In some tasks, one individual may perform as well as another, be observed to use the same overt behaviour and be thought to use the same cognitive approach, but actually be using a different cognitive strategy.

In actual fact, the use of a different cognitive strategy can in fact be indiscernible at the behavioural and cognitive level. Fortunately, the advent of fMRI means that differences in cognitive strategy can now be identified at a functional level. In this thesis, the term 'functional' refers to measurement of the brain activation associated with the behavioural or cognitive strategy. There are numerous methods of functional measurement, but in this thesis the term functional refers to the qualitative and quantitative measurement of brain activation using fMRI. Functional approaches can be used to measure the neural activation associated with any cognitive task that can be undertaken within the scanner environment. FMRI methodologies such as ROI analysis can be used to determine activation differences during the cognitive strategies adopted by different individuals as they perform a prescribed task.

The integration of functional, behavioural and cognitive models of explanation to identify the neurobiological underpinnings of neurodevelopmental disorders has previously been termed 'integrative' research (19). Ultimately, integrated approaches that constrain and inform each other (4, 5) are required to establish actiologically valid models that explain and elucidate the neurobiological actiology of SCI as seen in ASD.

7.3 Model of Social Communication Impairment – Evolutionary Level

Social communication is a sub-component of social behaviour, which involves an understanding of the verbal and non-verbal communicative behaviour of other people. Social communication is postulated to have emerged due to the need to cope with an increasingly complex social environment. The greatest information processing load imposed on humans is reportedly social interaction (333). Social interaction involves two types of behaviour - social affiliative and social strategic behaviour. Researchers have argued that affiliative behaviour is likely to represent a discreet system (334) and be distinct from the development of strategic social skills that underpin social communication (335, 336). Individuals with SCI can, but often do not, show social affiliative behaviour; however, they cannot meet the processing demands of social strategic behaviour. Social strategic behaviour requires social learning by the acquisition of behaviour patterns through observation or interaction with another person (337). Social imitation and social attention are key in the acquisition of social behaviour and have both been shown to be abnormal in autism (318, 338, 339). The developmental of social groups has been argued to have resulted in the development of language (340), indicating that non-verbal communication predates verbal communication in human evolutionary development. Indeed, social communication is postulated to have required the evolution of a complex brain system termed the 'social brain' (341). The social brain includes the temporal and frontal cortex and regions of the limbic system such as amygdala. The social brain is reported to confer the ability to infer the mental states of others, and utilise this knowledge in order to maximise social and, hence, evolutionary success. The ability to utilise social knowledge in this way has been termed 'Machiavellian intelligence' (342).

7.4 Model of Social Communication Impairment – Development Level

Social communication is a developmental concept and younger children are reported to have higher scores on quantitative measures of autistic symptomatology (14). Non-verbal social communication predates verbal social communication in infant development. Social communication, for the purposes of

this thesis, refers to non-verbal social communication and the specific set of capacities by which emotion, cognitive and perceptual information is transmitted by non-verbal means such as facial expressions. Typically developing infants are socially motivated and have the immediate capacity to begin establishing a social relationship with their caregivers. There is developmental evidence for an innate capacity for face perception (208) that strongly suggests that there are specialised neural mechanisms dedicated to face perception and that these mechanisms are different from object perception (343). Indeed, very young infants show a preference for the human face, and newborn infants will orientate toward the faces of their parents and demonstrate selective attention to social stimuli in the first months of life (344, 345). Temporal regularities develop at about three months of age in the pattern of mother-infant gaze (346). Facial expressions and eye contact are the most frequent modes of communication between the pre-verbal infant and his or her mother, and by the end of the first year of life typically developing infants have established a coherent repertoire of non-verbal social behaviours (347). Recent studies suggest that the visual processing strategy used in the communicative exchanges undergoes developmental changes (348), supporting a developmental trajectory for face processing and social communication in typical development, both of which are abnormal in ASD.

7.5 Model of Social Communication Impairment – Behavioural Level

Various research groups consider SCI the primary behavioural deficit in autism (150, 349). However, SCI is not unique to autism, and occurs in: many other neurodevelopmental and neuropsychiatric disorders (350); behaviour disorders such as conduct disorder (351); and, as a dimension in the general population (14). Over time the perceived wisdom on the specificity of a deficit for a particular disorder has changed, and the existence of SCI in other diagnosis is now not thought to preclude SCI as a primary behavioural deficit in autism. Indeed, the primacy of the cognitive construct for SCI in autism is now viewed as less important than the primacy of the cognitive construct as an explanation for SCI across diagnoses and emphasis is now placed on the association between the behaviour domain, the cognitive construct and functional correlates across diagnosis. Behaviour historically has been measured categorically; however, there is now an onus toward developing ways of measuring dimensions of behaviour, in particular the quantification of aetiologically valid dimensions of behaviour. Both categorical and dimensional behavioural approaches to the measurement of behaviour are reviewed below.

7.5.1 Categorical Approaches

Historically, disorders in psychiatry have been categorically defined by imposing an arbitrary cut-off, above which individuals are said to be affected, and below which individuals are said to be unaffected by the disorder. This is appropriate for some dichotomous disorders that either exist or do not exist. However, individuals with SCI exist on a continuum or spectrum of 'affectedness' (78). Indeed, one of the characteristics of SCI is the degree to which SCI symptom severity, intellectual ability and language impairment varying widely across individuals.

Research studies have focused on categorical approaches to the behavioural delineation of disorder and on determining the threshold at which the individual is undisputedly affected, thus, ensuring diagnostic

reliability and validity between groups diagnosed as having the disorder. Categorical symptom-based methods in autism have been designed to produce cut-offs of discontinuity between individuals with autistic conditions and the general population. Efforts at specifying and identifying behavioural differences between individuals with ASD and typically developing individuals have involved the use of increasingly detailed clinical infantries and observation schedules. However, these categorical behavioural approaches to autism have been largely unsuccessful in determining the biological underpinnings of ASD, and the aetiology of autism remains elusive.

7.5.2 Dimensional Approaches

Studies attempting to classifying milder, but clinically handicapping, forms of ASD have investigated whether 'social communication' could be used to assess severity of symptoms in ASD (352) and these studies support that this may be useful in describing the problems of autistic people (353, 354). Behavioural approaches have turned to the dimensionalisation of ASD, although it remains unclear whether autism is best conceived of as: a unitary syndrome; a set of related but distinct subtypes; or, a spectrum of abnormalities (355). Dimensional behavioural approaches acknowledge that, what may seem like disparate behaviours, may actually group together when explaining the variability between individuals and have common underlying aetiologies. Modelling and quantifying continuously distributed characteristics can be a more powerful approach to aetiological analysis as these methods reflects the true state of nature rather than a reductive dichotomy of 'affected' and 'non-affected' diagnostic status (326).

Researchers have started to focus on the identification of behavioural dimensions that explain the variance in individuals with ASD. Factor analysis, a method of modelling, offers the opportunity to identify the factors or dimensions of behaviour that explain the variance in a behavioural model. Tanguay and colleagues undertook factor analysis of autistic symptomatology measured in 63 individuals with PDD and, using 28 items related to current social communication from the ADI-R, identified three social communication domains: joint attention; affective reciprocity; and, TOM (2). The reported factor structure supports that two of the three behaviour domains in the current diagnostic criteria for autism (communication impairment and social impairment) are not independent domains (356) and provides evidence to support that social impairment and communication impairment domains are distinct from the repetitive behaviours domain in ASD. The independence of repetitive behaviours domain is also supported by a recent study by Silverman and colleagues (357).

In a another recent factor analysis study using the SRS, Constantino and colleagues defined social reciprocity symptoms at different levels of severity, with autistic symptoms anchoring the more 'affected' end of the scale. Constantino and colleagues found that all symptoms factored on to one autistic symptom dimension fitting with the notion of autism as a unitary syndrome (358). Attempts to capture the distribution of autism symptoms related to social processes have shown promise in identifying a spectrum across varied populations (3). The use of a dimensional behavioural approach to quantify autistic symptomatology has produced some preliminary successes in aetiological studies of ASD. Genetic analyses of familial quantitative traits such as non-verbal communication in families with

at least two sibs with ASD found quantitative trait loci (QTL) at 1p13-q12, 4q21-25, 7q35, 8q23-24, and 16p12-13 indicating that genes at these loci may contribute to the variation in non-verbal communication among those with ASD (359). However, the fine mapping of loci to determine the specific aspects of the autism diagnosis encoded, and identify susceptibility genes that are risk factors for that particular factor, is time consuming and difficult using 'bottom up' approaches. Recent genetic studies, have used the SRS to quantifying SCI in autistic individuals. Indeed, one such study using the SRS scale found several statistically significant genetic locus related to SRS score, highlighting the potential utility of this dimensional scale in identifying susceptibility genes for SCI in autism (360). However, fine mapping to determine which genes in these genetic loci are risk factors for SCI is hampered by the lack of explanatory model(s) for SCI. Hypothesis-driven approaches that identify aetiologically valid genetically mediated behavioural phenotypes, for which cognitive and functional levels of explanation can be identified, have the advantage that the behavioural dimension under study is constrained in this type of 'top-down' approach and, therefore, the phenotype to which the genes relate is already known.

7.6 Model of Social Communication Impairment – Cognitive Level

The key criteria that have been used to judge the primary nature of cognitive deficits in autism are universality and uniqueness within the diagnosis. However, explanatory value and hence, causal precedence have become increasingly emphasised. Therefore, primacy of reduced expertise in the attribution of emotion from facial expression for all symptom domains in autism would now be regarded as less important than the explanatory validity of reduced expertise in emotion attribution from facial expression for SCI specifically in any explanatory model.

Faces are probably the most important visual stimulus for human beings, certainly in terms of social interactions. Yet despite the fact that facial expression processing is one of the basic building blocks of social cognition, and the first step in the social communication process, currently cognitive models of the development of the ability to attribution emotions from facial expressions remain limited. Once a given social target is identified the next step in the social communication process is to determine if that target is approachable and willing to interact. This type of social information is gleaned from changeable aspects of the face, such as the eyes and mouth, which develop emotional expressions such as happiness and anger. Models of facial expression processing have favoured a distinction between the perception of static aspects of faces and the perception of dynamic aspects of the face (231). However, overlap in the regions of the brain that support the visual processing of faces and attribution of emotion from dynamic facial expressions (361) suggests that the right FG is involved in the configural processing of dynamic and static face percepts (261). There is also evidence that the visual processing of face percepts has a developmental trajectory related to the development of configural processing in typically developing individuals (348).

Inversion is one of the most common ways to investigate configural versus feature-based processing of faces and has been used to infer expertise for upright (non-inverted) versus inverted faces in adult populations (327, 328). Inverting face stimuli disrupts the configural processing of the face, and has a detrimental effect on the ability to process faces configurally (206). Inverted faces are recognised more

slowly and with higher error rates than upright faces (362, 363) and this decrement in performance is more marked for faces than other objects. Several studies suggested that the inversion effect is due to disruption of information processing specific to faces, or other stimuli with which adults have a comparable level of expertise (16). The development of rapid perceptual processing of faces during face recognition tasks has been associated with a transition from feature-based to configural processing and an associated increase in the magnitude of the inversion effect (242, 364). Although some studies have reported that the face inversion effect is absent in young children (202), others have found that subtle effects of inversion are detectable even in infancy (365) and significant inversion effects have been reported in children from 4 to 7 years of age (196, 211, 366-368). Configural processing of faces and the inversion effect have also been shown using measures of facial preference and gender recognition (369). Thus, the inversion effect and, by inference, configural processing have been found to be present in young school-aged children and infants and most studies that examined the development of face inversion have reported increasing inversion effects with age (196, 211, 370). These studies provide evidence that the configural processing of faces differs between inverted and non-inverted faces from early in development (371). Incorporation of an inverted task in any paradigm that is thought to involve configural processing allows interrogation of the inversion effect. Recent neuroimaging studies bring knowledge of the associated neural activation and support that non-inverted faces are processed holistically (372) or configurally (363) and that inverted faces are processed using feature-based information (229). Neuroimaging studies of face and facial expression processing are discussed in the next section.

7.7 Model of Social Communication Impairment – Functional Level

In terms of a functional explanatory model for the SCI there are strong functional models of face processing in typical (187) and autistic populations (18, 188) raising the possibility that a neurofunctional social endophenotype or marker is on the horizon (373). Neuroimaging studies have implicated the right FG in configural processing (348) and the ITG in the feature-based processing of faces (18).

7.7.1 Fusiform Gyrus and Configural Processing

When typically developing individuals view human faces brain activation occurs in the right FG located in the ventral temporal region. The right FG has been associated with 'global' analysis of faces and the development of expertise in the processing of faces (240). Facial expression studies also suggest that the right FG is sensitive to emotional valence showing increased activation when visual stimuli have emotional content or when a cognitive task requires attribution of emotion from facial expressions (314, 374).

Individuals with autism have been found to be less expert at the configural processing of faces and have been reported to have reduced FG activation when processing facial stimuli (6, 18, 249). Right FG has been correlated with social impairment as measured by the social impairment domain score on the ADI-R (276). Autistic children have also been reported to process static images of human faces normally and inverted faces better, supporting the idea that they have a predisposition toward the processing of 'component' parts (249), but are able to configurally process faces as proposed in recent research on

enhanced local perceptual precedence (223). The right FG has been mainly associated with static facial recognition, but recent studies have also found reduced right FG when individuals with ASD attribute emotion from static facial expressions (8).

7.7.2 Inferior Temporal Gyrus and Object Processing

Consistent with the feature-based perceptual processing of faces, high functioning individuals with ASD have been reported to have reduced activation in the right FG (an area normally activated by typically developing individuals when processing inverted faces) and increased ITG activation (18). The ITG has been shown to be strongly associated with object-specific perceptual discrimination in typically developing individuals. However, the opposite pattern is seen in autistic subjects (375), who have been shown to activate the ITG when processing faces similar to the perceptual processing of objects in persons free from social disability (18). Feature-based processing is also associated with the inversion of objects for which the individuals has expertise and has been shown to occur in typically developing controls when faces are inverted (229).

7.8 Model of Social Communication Impairment – Genetic Level

To infer the genetic validity of a construct of unknown genetic aetiology, it is common to investigate for phenotypic similarities between FDR. FDR can express the phenotype above threshold for the disorder and, therefore, attract a diagnosis or express aspects of the phenotype sub-threshold for the disorder attracting the term 'broader phenotype'. The recognition of the broader phenotype in FDR in many disorders has led to the recognition that aspects of disorder are over-represented in the families of affected individuals or 'familial'. The broader phenotype and familiality provide evidence for heritability and are suggestive of an underlying genetic aetiology. Co-segregation of behavioural, cognitive and functional levels of explanation for the behavioural phenotype is suggestive of a common underlying genetic aetiology. However, co-segregation can also be because of the proximity in the genome of the genetic loci for the different levels of explanation.

The siblings of individuals with autism express aspects of the autistic phenotype (135). A recent study by Constantino and colleagues, using the SRS, found sub-syndromal autistic impairments among siblings of probands with PDD (376). Indeed, sub-threshold autistic social impairments in the parents resulted in a substantial shift in SCI in the child providing evidence for the inter-generational transmission of social impairment (377). Other studies also support that social communication is heritable. Scourfield and colleagues, examined social cognitive skills in 5-17 year old twins using parent report data and found it to be highly heritable (378). Heritability estimates range from 27% in toddlers (379) up to 68% in older children and adolescence (378). To reduce the heterogeneity in autism, it would be important to determine if dimensions of autism are heritable and to collate evidence for a common cognitive, functional or genetic aetiology (357, 380). Co-segregation of these levels of explanation would provide evidence for a common underlying genetic aetiology. Familiality can be usefully employed to identify if neurodevelopmental constructs are genetically mediated. Familiality comprises both the genetic and environmental factors that contribute to the trait in families, and is similar conceptually to 'broader' heritability. 'Narrow' heritability is used to refer to additive genetic effects that contribute to the

expression of the trait and is usually determined using twin design studies. Familiality can be estimated from sib-sib correlations in population samples or by using genetic variance components analysis in families.

Surprisingly, little attention has been paid to the familiality or heritability of neurocognitive deficits that underpin the social manifestations of neurodevelopmental disorders (381) and the heritability of emotion attribution deficits has not been published to date. Dorris and colleagues examined emotion attribution from the eyes region of the face in the siblings of individuals with ASD and found that siblings had poorer performance than age matched typically developing controls (168), supporting the expression of emotion attribution deficits in the siblings of autistic probands. Baron-Cohen and colleagues undertook a pilot fMRI study looking at the neural correlates of emotion attribution from the eyes region of the face in the parents of individuals with ASD and found atypical activation in the mothers and fathers of individuals with ASD (382). Both these studies support the notion of emotion attribution deficits as part of the broader phenotype in the FDR of individuals with ASD. Expression of both SCI and emotion attribution deficits or co-segregation in the same individuals would suggest that they have a common underlying aetiology. Familiality would support that they are genetically mediated. Family studies are required to determine the familiality and ensure co-segregation of any explanatory constructs for SCI. Population and/ or family case-control studies are required to determine: if the prevalence of SCI is greater in families of individuals with SCD when compared to the families of typically developing individuals; and, if SCI and emotion attribution are over-represented within the families of individuals with SCD compared to the families of typically developing individuals. Although the genetic level of explanation is beyond the scope of the studies presented in the thesis, genetic validation of the constructs would be important in any integrated explanatory model for SCI in ASD.

7.9 Integrated Explanatory Model of Social Communication Impairment

The reviewed literature suggests that the use of categorical diagnostic classification systems based on behaviours may be sub-optimal for the identification of individuals with autistic symptomatology and supports the use of quantitative approaches rather than cut-offs based on 'caseness' in further integrated research (383). Quantifying independent constructs/ domains in the autism phenotype that are, potentially, more aetiologically homogeneous, rather than continued reliance on the heterogeneous categorical phenotype, should make it easier to identify underlying aetiologies (66). Cognitive and function levels of explanation that constrain and inform potential models for SCI are required to identify aetiological valid explanations for SCI. Previous cognitive models of SCI were constructed when little was known about the neurobiological basis of human social behaviour. Despite the centrality of social dysfunction in the definition of autism, the characterisation and quantification of the SCI necessary to direct research has not occurred (4). The dimensional studies quantified autistic symptomatology to enable investigation of the validity of reduced configural processing as an explanation for: reduced expertise in the attribution of emotion from dynamic facial expressions; and, the SCI seen in high functioning young men with SCD. Studies to date have not examined the relationship between the neural correlates of emotion attribution from facial expressions and SCI in high functioning young men with SCD. It remains unclear whether there is a proportional relationship between behavioural, cognitive or

functional levels of explanation for SCI as seen in autism (e.g. *'Does reduced right FG specialisation for configural processing reduce expertise in the attribution of emotion from dynamic facial expressions and predict a greater degree of SCI?'*). Integrated explanatory models, which incorporate behavioural, cognitive and functional levels of explanation based on constructs such as configural processing, which have an evolutionary and developmental validity, are needed to determine the underlying aetiology of SCI.

7.10 Aims of Dimensional Studies

The aim of the dimensional studies presented in this thesis was firstly to determine the relationship between SCI measured categorically and dimensionally. Then secondly to determine any relationships between behavioural, cognitive and functional levels of explanation for SCI, to further inform an aetiologically based explanatory model for SCI in ASD. The aim of quantification of autistic symptomatology was to allow the relationship between SCI, expertise in the attribution of emotion and activation in informative ROI during the attribution of emotion from dynamic facial expressions to be investigated. The specific aim of the fMRI study was to further investigated if right FG specialisation for configural processing and/ or reduced expertise in the attribution of emotion from facial expressions might explain SCI in individuals with SCD. The fMRI study also aimed to determine if activation patterns in the ITG ROI provided evidence suggestive of a predisposition toward the feature-based processing of non-inverted faces in high functioning young men with SCD and their brothers.

7.11 Rationale of Dimensional Studies

The overarching rationale behind the dimensional studies presented in this thesis was that a dimensional behavioural approach to SCI would facilitate the identification of the cognitive and functional correlates of SCI. Specifically, dimensionalisation of SCI would allow investigation to establish if SCI is related to expertise in the attribution of emotion from dynamic facial expression and right FG specialisation for the configural processing of facial expressions in young men with SCD. The quantification of SCI across diagnostic boundaries was undertaken to identify any cognitive and/ or functional correlates of SCI. The right FG has been proposed as a functional marker or 'endophenotype' for the social impairment in ASD (326); however, the mechanism by which the right FG would be informative as an endophenotypes has not been identified. Reduced specialisation of the right FG for configural processing during the attribution of emotional from dynamic facial expressions represents a potential mechanism by which the right FG could explain SCI. Combined with the use of dimensional measures to quantify affectedness in individuals with SCI across diagnostic boundaries, the identification of such a relationship would validate the use of emotion attribution paradigms as a cognitive and right FG activation as a functional explanation for SCI with which to ascertain more homogeneous groups potentially, increasing the power of future etiological studies of SCI.

7.12 Hypothesis of Dimensional Studies

- Individuals with SCD, who fulfil an ADI-R diagnosis of autism, would have quantitatively greater SCI than those who do not fulfil an ADI-R diagnosis of autism.

- Individuals with SCD would be less expert than their brothers in the attribution of emotion from non-inverted (upright) dynamic facial expressions. This would be related to reduced right FG ROI specialisation for the configural processing of dynamic facial expressions and, potentially, enhanced local perceptual precedence in the proband group.
- Individuals with SCD would be as expert as their brothers during the attribution of emotion from inverted facial expressions related to comparable neural activation during the attribution of emotion inverted dynamic facial expressions.

7.13 Methodology of the Dimensional Studies

To address the aim in the dimensional studies, 60 high functioning young men with SCD between the ages of 10-18 with a SRS score greater than 60 were recruited as previously described. These high functioning young men with SCD were characterised using two qualitative measures of autistic symptomatology called the SCQ and the ADI-R. The SCQ and the ADI-R scores were used to determine if these high functioning young men with SCD qualitatively fulfilled criteria for ASD and autism respectively. SCI was then quantified as a dimension of behaviour, and qualitative measures used to determine if ADI-R diagnosis identified distinct groups based on severity of SCI. In the first dimensional study, the severity of SCI in individuals with and without an autism diagnosis was compared. The second dimensional study used an event-related fMRI experimental design and acquisition parameters to determine if there was a relationship between activation in the right FG and ITG ROI. These ROI are involved in the perceptual processing of non-inverted and inverted faces respectively, and expertise in the attribution of emotion from non-inverted and inverted dynamic facial expressions in high functioning individuals with SCD and their brothers.

Chapter 8 Study 3: Comparison of Qualitative and Quantative Approaches to Autistic Symptomatology in Individuals with Social Communication Difficulties

Summary of Study 3

Social communication has been reported to exist as a dimension of behaviour in the general population, and autism has been conceptualised as the upper extreme of this social communication dimension (15). Previous studies of SCI have focused on autism (184); however, SCI has been conceptualised as the 'core' deficit in all forms of ASD (2, 384). In this study, high functioning young men with SCD (probands) were recruited irrespective of whether they fulfilled criteria for an ADI-R diagnostic of autism to determine if they had similar SCI to that seen in autism. This study quantified autistic social symptomatology in young men with SCD and investigated to determine if diagnosis differentiated quantitatively distinct groups based on degree of SCI. This study was undertaken to determine if there was a significant difference in the severity of SCI associated with different diagnostic categories and to facilitate comparison of the different samples recruited for the categorical and dimensional fMRI studies presented in this thesis.

Sixty probands between10-18 years identified as having SCD by their respective parents were characterised using two qualitative measures called the SCQ and the ADI-R, and a quantitative measure of autistic social symptomatology called the SRS. All probands were above threshold on the ADI-R social impairment sub-domain for a diagnosis of autism, and had SRS scores in the range previously reported for PDD-NOS (13). There was no significant difference in SRS scores based on clinical diagnosis or ADI-R diagnosis of autism. In this study, all the high functioning young men with SCD had a qualitatively similar SCI to that seen in autism and quantitatively similar levels of SCI to that previously reported for PDD-NOS (14) supporting: that the SCI is similar to that seen in ASD; and, comparison of the findings from the categorical and dimensional fMRI studies. ADI-R diagnosis of autism did not differentiate groups with quantitatively distinct levels of SCI. Individuals with SCD had SCI that was: qualitatively similar to autism; and, in the range of severity reported for PDD-NOS (13). The findings of this study support transgression of diagnostic boundaries, and study of SCI as a dimension of behaviour, to elucidate the functional aetiology of SCI.

8.1 Introduction to Study 3

Social communication has been described as the specific set of neurodevelopmental capacities through which cognitive and emotional information is communicated using facial expression, emotional gesture and prosody of speech (2). SCI would be expected to: relate to impairment in these neurodevelopmental capacities; pertain to the autistic social behaviour (354, 385, 386); and, exist across and beyond diagnostic boundaries, but the relationship between SCI and the underlying neurodevelopmental capacities remains elusive. Individuals with ASD are known to have SCI and are reported to have difficulties attributing emotion from static facial expressions (296); however, categorical diagnoses make investigation of the relationship between SCI and underlying neurodevelopmental capacities difficult. The quantification of SCI is necessary if future aetiological studies are to elucidate the nature of the relationship between behaviour, cognition and function and determine the underlying aetiology of SCI.

According to DSM-IV the SCI seen in autism is common to all PDD diagnosis, including autism, AS and PDD-NOS. By inference the diagnostic classification systems provide support for the quantification of SCI across ASD. Indeed, SCI has been conceptualised as the 'core' deficit in all forms of ASD (2, 384). Studies of SCI have predominantly focused on autism and AS, which have specific diagnostic criteria, and studied them separately. High functioning individuals with SCI attract a diagnosis of HFA if there is a history of language delay and a diagnosis of AS if language development is normal. However, there is little evidence to substantiate diagnostic categories based on language acquisition (387). Also of importance, high functioning individuals, who do not fulfil criteria for HFA or AS diagnosis, but who have significant SCI often receive a diagnosis of PDD-NOS. PDD-NOS does not have specific diagnostic criteria and has been termed a diagnosis of exclusion (66). PDD-NOS has become a catch-all diagnosis for those with SCI who do not fulfil criteria for autism or AS (62), and individuals with PDD-NOS are commonly excluded from research. There are also many individuals who, despite significant SCD, are judged not to fulfil criteria for any PDD diagnoses. High functioning individuals with SCD are also diagnosed as having NLD (100) and semantic pragmatic disorder (101, 388). These diagnoses, which are not included in DSM-IV, have SCI as a diagnostic criterion and overlap with PDD. Individuals with SCI also often receive diagnoses such as ADHD and Tourette's disorder (389), which do not have SCI as a diagnostic criterion because of the hierarchical nature of diagnostic classification systems. Hence, the diagnosis that an individual with SCD receives is often arbitrary in terms of their SCI and many individuals with SCI are inadvertently excluded from SCI research.

The SRS, previously known as the Social Responsivity Scale, was made available by the developers - Constantino and colleagues prior to general release for use in the dimensional studies presented in this thesis (13). The SRS, is a quantitative measure of autistic symptomatology across the PDD spectrum, specifically autistic social symptomatology. Studies using the SRS suggest that autistic symptoms are continuously distributed in the general population with autism best conceptualised as the upper extreme of a continuously distributed constellation of deficits in social communication behaviour (14). Although DSM-IV requires symptoms above threshold in three criterion domains for the diagnosis of autism, the quantification of autistic symptomatology using the SRS was found to be consistent with the existence of a single, continuously distributed aetiological factor underlying autistic symptomatology in all three

DSM-IV symptom domains (358). Parsimoniously, these studies using the SRS suggest that diagnostic and symptom domain boundaries may not be biologically meaningful and support the quantification of autistic symptomatology across PDD. The measurement of SCD as a quantitative trait could potentially: promote the inclusion of individuals with similar SCI across diagnostic boundaries; ensure the inclusion of individuals with sub-threshold SCI; provide information on the severity of the SCI; and, increase the capacity of future research to investigate the aetiology of the SCI as seen in ASD.

8.2 Aims of Study 3

The aim of Study 3 was to investigate if clinical diagnoses differentiate quantitatively distinct groups based on SCI and facilitate comparison of the individuals recruited in the dimensional and categorical studies in Part II and Part III of the thesis. The study aimed to determine if high functioning young men with SCD had qualitatively similar SCI to that seen in autism; and, to quantify SCI to permit the dimensional fMRI study of SCI presented in this thesis.

8.3 Rationale of Study 3

Previous studies of SCI have focused on categorical diagnoses such as autism, although social communication has been reported to exist as a dimension of behaviour in PDD and the general population (15) with autism anchoring the more affected end of the continuum. Therefore, high functioning young men with SCD who fulfil diagnostic criteria for autism could be expected to have quantitatively greater SCI than those who do not fulfil diagnostic criteria for autism. To date, no studies have transgressed diagnostic boundaries to determine if individuals with SCD, who fulfil criteria for autism, have SCI that is qualitatively greater than those who do not fulfil criteria for autism. Study 3 focused on the dimensionalisation of autistic social symptomatology in high functioning individuals with SCD and determined the relationship between SCI and ADI-R diagnosis of autism. The rationale was that quantification of SCI would allow investigation to determine if diagnosis differentiated groups based on SCI severity and effect the inclusion of all individuals with SCD in the dimensional fMRI study presented in the next chapter of this thesis. Quantification of SCI, measured as a dimension of behaviour, was also undertaken to facilitate comparison of the findings of the fMRI studies of high functioning individuals with ASD in Part II of the thesis with the findings of the fMRI study of high functioning individuals with SCD and their brothers in Part III of the thesis.

8.4 Hypothesis of Study 3

- Individuals with SCD would have qualitatively similar SCI to that seen in individuals with autism and quantitatively similar SCI to that reported for ASD populations.
- Individuals with SCD who fulfilled an ADI-R diagnosis of autism would have quantitatively greater SCI than those that did not fulfil an ADI-R diagnosis of autism as previously reported in studies of SCI measured as a dimension of behaviour.

8.5 Methodology Specific to Study 3

To address the aims of Study 3, 60 high functioning individuals with SCD, who had been recruited into an ongoing the genetic study at Stanford University, were studied. SCI, measured using the SRS, gave a quantitative (dimensional) measure of autistic symptomatology and the SCQ and ADI-R gave qualitative

(categorical) measures of autism symptomatology. The SCQ determined if the probands were above the SCQ threshold score for further screening for ASD. The ADI-R was used to determined if they fulfilled ADI-R criteria for autism using current and most abnormal ADI-R scores.

The probands were divided into their respective diagnosis: using clinical diagnosis as assigned by their clinician; PDD diagnosis based on the SCQ; and, autism diagnosis based on the ADI-R and differences in SRS scores explored between groups. Young men who did, and those who did not, fulfil ADI-R diagnosis of autism where compared to determine if an ADI-R autism diagnosis differentiated groups with quantitatively distinct SCI. The proband group was also divided into those that did, and those that did not, fulfil ADI-R criteria on the repetitive behaviour sub-domain and analysis undertaken to determine if SRS scores were different between these groups.

Previous studies with the SRS have focused on quantifying autistic symptoms within the boundaries of ASD. This study used the SRS to quantify the severity of the SCI in young men with SCD across diagnostic categories. The SRS scores for young men with SCD with and without an autism diagnosis were compared and SRS scores compared to those previously published for PDD-NOS (14).

8.6 Results of Study 3

8.6.1 Demographic and Neuropsychological Results

The proband group consisted of 56 probands who were Caucasian, and 4 probands who were mixed race - 1 Caucasian/ Asian, 1 Hispanic/ Caucasian, 1 Caucasian/ Native American and 1 Hispanic/ Pacific Islander. The families' socio-economic status was skewed toward high-income households (median income = $125-150,000 dollars) and all families who participated were resident in Northern California. The 60 probands had a mean age of 13 yrs, ranging from 10-18 yrs, and average to above average cognitive function [FSIQ = 123, SD +/- 15.5; VIQ = 125; SD +/- 17, PIQ = 116; SD +/- 14.0].

There were 50 probands who had a received a PDD diagnosis from their own clinician: 39 had an AS diagnosis; 7 had a HFA diagnosis; and, 4 had a PDD-NOS diagnosis. There were 10 probands, who did not have a clinical PDD diagnosis; 7 had an NLD diagnosis; and, 3 had no diagnosis. The proband group included 39 individuals who were receiving medication: 28 were receiving anti-depressant medication; 7 were receiving stimulant medication; 8 were receiving anxiolytic medication; 4 were receiving anti-epileptic medication; and, 1 was receiving anti-psychotic medication.

8.6.2 Behavioural Measures Results

8.6.2.1 Social Communication Questionnaire

In this sample, 45 probands were above the SCQ threshold score for PDD: 40 of whom had received a PDD diagnosis from their own clinician; 4 had a diagnosis of autism; 32 had a diagnosis of AS; and, 4 had a diagnosis of PDD-NOS. There were 5 probands who were above the SCQ threshold score of 15, but had not received a PDD diagnosis from their own clinician. There were 3 probands who had a clinical diagnosis of NLD and 2 probands who had no clinical diagnosis.

8.6.2.2 Autism Diagnostic Interview-Revised - Most Abnormal Behaviour Scores

All probands were above threshold for qualitative impairment in the SCI behaviour sub-domain using most abnormal behaviour scores in the ADI-R algorithm. There were 42 probands who fulfilled ADI-R criteria for an autism diagnosis using the most abnormal behaviour scores in the ADI-R algorithm. There were 18 probands who did not fulfil all three ADI-R sub-domains using the most abnormal behaviour scores in the ADI-R algorithm: 3 were below threshold on the communication impairment sub-domain; 17 were below threshold on the repetitive behaviours and restricted interest sub-domain; and, 2 did not have an abnormality of development evident before 36 months.

There were 50 probands who had received a PDD diagnosis from their own clinician. Of these 34 fulfilled, and 16 did not fulfil, ADI-R criteria for autism using the most abnormal behaviour score in the ADI-R algorithm. There were 10 probands who had not received PDD diagnosis from their own clinician. Of these 8 fulfilled, and 2 did not fulfil, ADI-R criteria for autism using the most abnormal behaviour score in the ADI-R algorithm.

8.6.2.3 Autism Diagnostic Interview-Revised - Current Behaviour Scores

Using current behaviour scores in the ADI-R algorithm 32 probands fulfilled an autism diagnosis. All probands were above threshold for a diagnosis of autism in the SCI sub-domain using current social impairment sub-domain scores in the ADI-R algorithm. There were 28 probands who did not fulfil all three ADI-R sub-domains based on current behaviour: 6 were below threshold on the communication impairment sub-domain; 26 were below threshold on the repetitive behaviours and restricted interest sub-domain; and, 2 did not have an abnormality of development evident before 36 months.

There were 50 probands who had received a PDD diagnosis from their own clinician. Of these 27 fulfilled ADI-R criteria for autism using current behaviour scores in the ADI-R algorithm. There were 10 probands who had not received a PDD diagnosis from their own clinician, 5 of whom fulfilled ADI-R criteria for autism using the current behaviour scores in the ADI-R algorithm.

8.6.2.4 Social Responsivity Scale Score

The proband group had a mean SRS score of 106 (SD = 18.77) and SRS scores in the range 67-145. The mean SRS scores and SRS score ranges of the proband group for different clinical diagnoses are given in Table 8-1. The SRS was not correlated with age or IQ in the proband group. The SRS score was significantly correlated with the current social impairment score ($r = 0.407$, $p = 0.001$) and the most abnormal social impairment score ($r = 0.356$, $p < 0.005$), but not with the current or most abnormal communication impairment score or the current or most abnormal repetitive stereotyped behaviours score on the ADI-R. There was no significant difference in SRS scores across clinical diagnoses [$F(5, 54) = 0.495$, $p = 0.779$] or medication status [$t(1, 58) = 1.06$, $p = 0.293$]. There was no significant difference in SRS score [$t(1, 58) = -1.63$, $p = 0.107$] for those probands who did have a PDD diagnosis versus those that did not have a PDD diagnosis based on SCQ.

Table 8-1 Social Responsivity Scale Scores for Clinical Groups

Clinical Diagnosis	Number	Range	Mean	Std. Deviation
No diagnosis	3	73–106	93	17.6
Autism	7	69-137	103	27.3
Asperger's Syndrome	39	67-145	108	18.0
PDD-NOS	4	74-114	99	17.3
NLD	7	82-132	108	17.5

Table 8-1 represents the Social Responsivity Scale Scores for individuals with pervasive developmental disorder, non-verbal learning disorder and no diagnosis.

Interestingly, probands who met ADI-R diagnostic criteria for autism using the most abnormal behaviour scores in the ADI-R algorithm did not have significantly different mean SRS scores [$t(58) = 0.255$, $p = 0.800$] when compared to those that did not have an ADI-R autism diagnosis. This was also true of probands who met ADI-R autism criteria using current behaviour scores, who also did not have a significantly different SRS scores [$t(58) = -0.534$, $p = 0.596$] when compared to those that did not have a diagnosis (Figure 8-1).

Figure 8-1 Social Responsivity Scale Scores for Clinical Groups

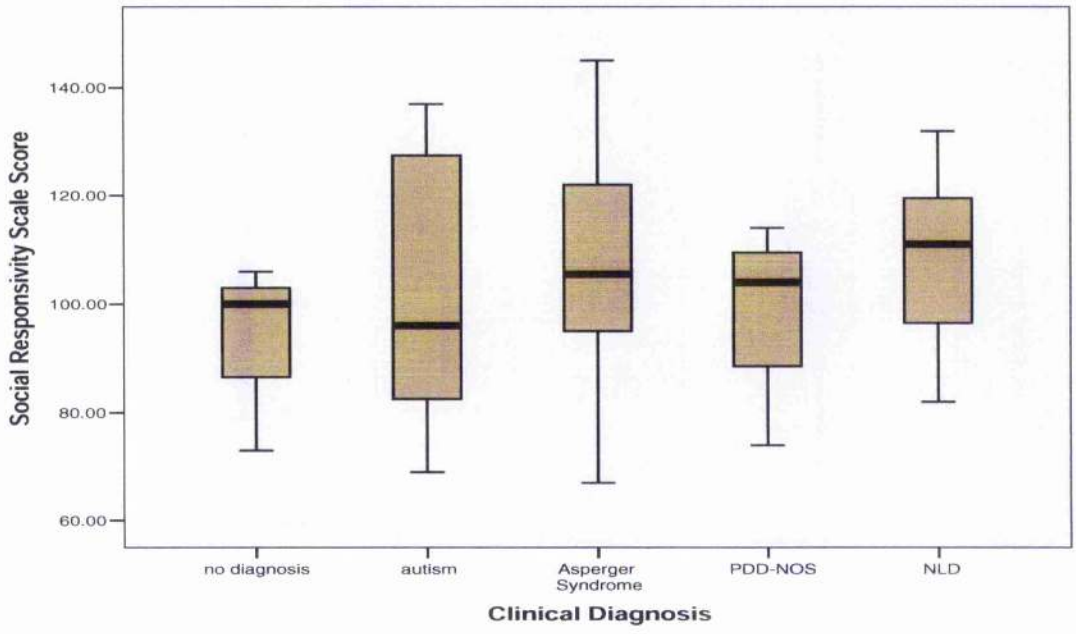


Figure 8-1 represents the Social Responsivity Scale scores for high functioning individuals with social communication difficulties with different clinical diagnosis.

8.7 Data Interpretation 3

This study characterised a high functioning group of young men with SCD using qualitative and quantitative measures of autistic symptomatology. The participants in this study were predominantly Caucasian and from families of high socio-economic status living in Northern California. Despite high average intelligence, the parents of these high functioning young men identified that they had marked SCD. Although a PDD diagnosis was not required for participation in the study, 50 probands had received a PDD diagnosis from their respective clinicians: 39 had a diagnosis of AS; 7 had a diagnosis of HFA; and, 4 had a diagnosis of PDD-NOS. There were 10 young men with SCD who did not have a PDD diagnosis: 7 had a diagnosis of NLD; and, 3 had no diagnosis. However, clinical and PDD diagnosis did not differentiate groups in terms of SCI and all the high functioning young men with SCD had levels of SCI in the range previously reported for PDD (14).

There were 45 high functioning young men with SCD who scored above 15 on the SCQ, an extensively used parent-completed screening instrument for the diagnosis of PDD. Interestingly, 5 probands who had not previously had a PDD diagnosis from their own clinician scored above 15, and 5 probands who had previously attracted a PDD diagnosis from their own clinician did not score above 15 using the SCQ. The SCQ has limited ability to measure circumscribed interest patterns (23), which are the most likely manifestation of repetitive behaviours in high functioning individuals with SCD. Therefore, the use of the SCQ to screen for PDD diagnoses in these high functioning young men with SCD may explain the diagnostic discrepancy between clinician and screener in this study. In addition, the criteria in the current diagnostic classification systems are open to individual clinician interpretation and the diagnosis in effect subjective, which might also contribute to this discrepancy between SCQ score and diagnosis.

All probands fulfilled the social impairment sub-domain threshold for autistic social impairment using behaviour between 4-5 years of age and current behaviour scores in the ADI-R algorithm. This suggests that the SCI in individuals with SCD are qualitatively similar to the SCI seen in autism and that SCI is a pervasive developmental domain. Interestingly, 42 high functioning young men with SCD actually fulfilled ADI-R criteria for a diagnosis of autism based on behaviour between 4-5 years of age, and only 32 young men still fulfilled ADI-R criteria for autism when this was based on current behaviour. The reduction was related primarily to fewer individuals fulfilling criteria for the ADI-R repetitive behaviour sub-domain when current behaviours were used in the ADI-R algorithm and is discussed later.

Many more young men with SCD fulfilled criteria for an ADI-R diagnosis of autism than expected from the collated clinical diagnoses. Differences between the ADI-R and DSM-IV classification criteria for a diagnosis of autism offer possible explanation for these diagnostic inconsistencies. According to the DSM-IV classification, autism is distinguished from AS by delayed language development - defined as delay in the use of single words by age 2 years or use of communicative phrases by age 3 years. However, in the ADI-R, a verbal individual can fulfil ADI-R criteria for autism on the communication sub-domain if they have a lack of varied spontaneous make-believe or social imitative play, and fail to initiate or sustain conversational exchange. An individual can meet diagnostic criteria for autism if a developmental abnormality was evident at, or before, 36 months in any one of the three sub-domains of the ADI-R. The ADI-R communication sub-domain captures social or 'pragmatic' language impairment

and, therefore, individuals with AS can satisfy language impairment criteria for an ADI-R diagnosis of autism, despite being considered clinically to have normal language development and clinically considered to have AS. Some would contend that individuals with AS who are deemed clinically to have normal language development, should actually be considered to fulfil criteria for an autism diagnosis because of their pragmatic deficits (390). Thus, individuals can have abnormalities of development and communication other than language delay in the first 36 months and attract an ADI-R diagnosis of autism, yet using DSM-IV would attract a clinical diagnosis of AS or PDD-NOS. These differences in diagnostic criteria have considerable implications on inclusion/ exclusion in research studies, and present further justification to investigate the quantification of symptom dimensions across diagnostic boundaries.

The DSM-IV classification system states that for a clinical diagnosis of AS, an individual need only have one of four types of repetitive behaviour, as opposed to the three out of four types of repetitive behaviour required to fulfil ADI-R criteria for a diagnosis of autism. Most of the young men with SCD in this study, who had received a DSM-IV diagnosis of AS, did not fulfil ADI-R criteria for autism because they exhibited insufficient repetitive behaviours. As mentioned the number of individuals who fulfilled criteria for the ADI-R repetitive behaviour sub-domain reduced when current behaviours were used in the ADI-R algorithm. This phenomenon has also been reported by Tanguay and colleagues (2) and suggests that repetitive behaviours may not be a pervasive domain in PDD. Similar to Tanguay and colleagues (391), this study also found high functioning individuals often had unusual preoccupations or circumscribed interests, but rarely had the more severe autistic symptoms required to fulfil the repetitive interests/ stereotypical behaviour sub-domain of the ADI-R. Interestingly, in this study the young men who did, and those that did not, fulfil ADI-R criteria for the repetitive behaviour sub-domain did not have significantly different SCI as measured by the SRS. These studies highlight that the exclusion of individuals who do not fulfil criteria for a diagnosis of autism on the repetitive behaviour sub-domain may need to be reconsidered in studies investigating the aetiology of SCI in individuals with SCD.

All participants with SCD in this study had an SRS score above 65, previously reported as the lowest score consistent with a diagnosis of PDD-NOS (13). There were 58 participants with SCD who had a SRS score falling within or above one standard deviation of the SRS mean score previously documented for PDD-NOS (101.1; SD $\pm$ 29.9). There were 32 high functioning young men with SCD who had a SRS score within one standard deviation of the mean previously documented for autism (117; SD $\pm$ 29.9). All young men with SCD had SRS scores above two standard deviation of the mean SRS score previously reported for typically developing individuals (mean = 29.9; SD $\pm$ 15.0) (13). Therefore, the high functioning young men with SCD, as identified by their parents, were found to have SCI that was qualitatively and quantitatively similar to the SRS scores previously reported for individuals with PDD.

Importantly, young men with SCD with different clinical diagnoses did not have significantly different mean SRS scores. In concordance, participants with SCD who were above threshold for a PDD diagnosis on the SCQ, and those who fulfilled an ADI-R diagnosis of autism did not have significantly different SRS scores from those that did not fulfil criteria on the respective instruments.

8.8 Key Findings of Study 3

This study found that all probands were above threshold on the ADI-R social impairment sub-domain for a diagnosis of autism and had SRS scores in the 67-145 range previously reported for PDD-NOS (13). There was no significant difference in SRS scores based on clinical diagnosis or ADI-R diagnosis of autism. In this study, all the high functioning young men with SCD had a qualitatively similar SCI to that seen in autism, and quantitatively similar levels of SCI to that previously reported for PDD (14).

8.9 Methodological Considerations of Study 3

The following methodological issues with respect to subject recruitment, behavioural measures, study design and procedure and statistical analysis need to be taken into account when considering the findings of this study.

8.9.1 Subject Recruitment

Individuals with other neurodevelopmental disorders were included in the study if they had SCI, as seen in autism. Barkley and colleagues reported that it is common for children with PDD-NOS to be initially given a diagnosis of ADHD (392). In one study it was reported that 74% of the children in their study diagnosed with PDD-NOS were originally diagnosed with ADHD (393). Another study showed that children with PDD-NOS and ADHD did not differ with respect to total number of autistic symptoms, general psychopathology, or attention difficulties (394). This overlap may be because some early signs of ADHD and PDD-NOS seem to be similar (394-396), although differences between the groups become more pronounced with age (397). There is no good evidence that the SCI in PDD is qualitatively different in individuals with ADHD, and so ADHD was not used as an exclusion criteria in this study.

To facilitate the study of SCI in isolation from language or general cognitive deficit, young men of normal to high IQ were recruited. Some of these young men had had delayed speech, but were included as early language delay is not predictive of autistic symptomatology in adolescent age groups (387); however, all had normal language at the time of the study.

8.9.2 Behavioural Measures

Both the ADI-R (a clinician interview based qualitative measure of autistic symptomatology) and the SCQ (a parent completed screener for the ADI-R) were used, and the correlation co-efficient calculated ($r = 0.89$) to provide additional evidence for the correct ADI-R diagnosis of autism in the young men with SCD.

Dimensional screening instruments based on autistic symptomatology represent an opportunity to improve the current recruitment strategy for genetic study. The use of dimensional screening instruments based on the diagnostic category of autism has disadvantages and advantages. The disadvantage, potentially, is the continued investigation of symptomatology without a proven biological basis, hence the need for aetiological studies. The advantages include comparison of results with the vast amounts of research literature that already exists on diagnostic phenotypes. As different diagnoses are used to express similar neurocognitive profiles by different professional groups and used interchangeably uncertainty exists regarding the specificity of the many diagnostic groupings. Transgression of

diagnostic boundaries and quantification in terms of SCI addresses these issues and represents a more optimal approach for genetic study in light of the current clinical and aetiological uncertainty surrounding diagnosis. Further cognitive and functional studies measuring SCI as a quantitative trait are required to determine if dimensionalisation of autistic symptomatology does identify a biologically valid construct that facilitates the aetiological study of SCI in young men with SCD. The SRS would be ideal for aetiological research if it captured a biologically validated aspect of the autistic social phenotype, as it can be quickly completed (20 minutes) by a carer or teacher, and gives a dimensional measurement of SCI allowing for the mapping of cognitive processes, brain function, and genes in future studies.

8.9.3 Study Design and Procedure

Ascertainment of an epidemiological sample would have represented the ideal recruitment strategy, but would have required the screening of large populations, which was beyond the scope and resources of this study. Epidemiologically ascertained samples would allow the prevalence of SCI in the general population to be determined and ascertainment of representative samples to determine the aetiology of SCI in the general population.

8.9.4 Statistical Analysis

The sample size was small when divided into clinical diagnostic groups; however, the comparison of the young men who fulfilled ADI-R autism, and those that did not fulfil ADI-R autism, afforded the degrees of freedom to detect significant differences between groups and found no significant difference in SCI between groups.

8.10 Conclusions and Implications of Study 3

As hypothesised all the high functioning young men with SCD had a qualitatively similar SCI to that seen in autism and quantitatively similar levels of SCI to that previously reported for ASD (14). Diagnosis did not differentiate groups with quantitatively distinct levels of SCI supporting the measurement of autistic social behaviour as a quantitative trait in the aetiological study of SCI. The dimensionalisation of autistic symptomatology allowed the rapid quantification of SCI in individuals with SCD qualitatively similar to that seen in autism. The quantification of autistic symptomatology using the SRS unified disparate diagnostic groups with qualitatively and quantitatively similar SCI onto a SCI continuum. Quantification of SCD across diagnostic boundaries avoided some of the diagnostic dilemmas that have become intrinsic to this field of research. Quantification of autistic symptomatology in this group of young men unified disparate diagnostic categories along a SCI continuum - in agreement with other recent studies that have examined the factor structure of autistic traits measured by the SRS (358). The quantification of SCI and transgression of diagnostic boundaries promoted inclusion of individuals with SCI and measurement of the severity of each individual's SCI increased the informativeness of those individuals for aetiological studies.

High functioning young men with SCD with an ADI-R diagnosis of autism, and those without an ADI-R diagnosis of autism, had quantitatively similar SCI contrary to the hypothesis that SCI would be quantitatively greater in those who fulfilled a diagnosis of autism as previously reported (14). This provides evidence that these high functioning young men with SCD have as severe SCI as high

functioning individuals with autism. Although autism would be best conceptualised as the upper extreme of a continuously distributed constellation of deficits in social and communication behaviour in the general population (14), this should not be taken to mean that the SCI in autism is necessarily more severe than the SCI in these high functioning verbal individuals. The SCI in these young men with SCD was in the same range as that previously published for PDD (14). This dimensional study lends support to those studies that have found autistic social symptomatology is best represented by one dimension and attributable one single underlying continuously distributed variable actiological factor underlying all three autism symptom domains (14, 358, 383).

Studies to date using the SRS support the quantification of autistic symptomatology to facilitate aetiological studies of SCD and circumvent the numerous diagnostic dilemmas inherent in research using diagnostic categories. These studies have not addressed the underlying aetiology of SCI as measured dimensionally by the SRS. Potentially, the quantification of autistic symptomatology in high functioning young men with SCD facilitates the investigation of cognitive and functional correlates of SCI. Quantification also effects the informative inclusion of individuals with qualitatively similar SCI below threshold for PDD diagnosis into aetiological studies. FMRI studies investigating the cognitive and functional levels of explanation for SCI are required and presented in Chapter 9, Study 4.

Chapter 9 Study 4: Attribution of Emotion from Dynamic Facial Expressions in High Functioning Individuals with Social Communication Difficulties

Summary of Study 4

The 10 young men with SCD and their brothers, who participated in the dimensional fMRI study, were recruited from a larger genetic study of SCI in 60 high functioning young men with SCD (probands) and their FDR (n = 241), which is ongoing at Stanford University. As part of this genetic study, all participants had their autistic symptomatology quantified using the SRS to give a measure of SCI. The proband group recruited at the time of this fMRI study had significantly greater SCI than all of their FDR groups. However, the father group also had a significantly greater SCI that the mother, male sibling and female sibling groups. High functioning young men with SCD were recruited into the fMRI study if they had brothers within four years of age and fulfilled the fMRI study inclusion criteria, hence, ten brother pairs performed the DFEP. The neural correlates and associations of SCI were then determined during the attribution of emotion from non-inverted and inverted dynamic facial expressions in hypothesis-driven ROI, chosen *a priori*, in these ten brother pairs. The fMRI study found that SCI was directly correlated with accuracy in the attribution of emotion across both proband and brother groups in the non-inverted, but not the inverted, facial expressions. There was a trend towards SCI being correlated with response time in the inverted condition of the DFEP. The proband group was as accurate as the brother group in the attribution of emotion from non-inverted and inverted facial expressions. However, there was a trend toward a significantly longer response time in the proband group in the non-inverted facial expression condition of the DFEP. Right FG activation was directly correlated with SCI in the non-inverted and indirectly correlated with SCI in the inverted condition of the DFEP. The proband group activated significantly greater right FG activation than the brother group to achieve a comparable performance in the non-inverted condition of the DFEP. The proband group also required to activate significantly less right FG activation than their brothers to achieve a comparable performance in the inverted condition of the DFEP. ITG activation was directly correlated with response time in the inverted condition of the DFEP. However, there were no significant differences in ITG activation between groups in either the non-inverted or the inverted condition of the DFEP. The findings of this dimensional fMRI study provide evidence in support of the right FG specialisation for the configural processing of face percepts. Right FG hyper-responsiveness may reflect the need for greater recruitment of right FG in individuals with ASD to compensate and achieve the comparable configural processing of facial expressions in the non-inverted condition of the DFEP. The hypo-responsiveness of the right FG to achieve comparable expertise in the attribution of emotion when the condition did not require configural processing for its successful completion provides further evidence in support of a predisposition toward atypical processing in individuals with ASD when configural processing is not necessary for the successful completion of the task. The findings of the dimensional fMRI study provides evidence that these high functioning individuals with ASD are able to configurally process face percepts as previously proposed in enhanced local perceptual precedence hypothesis (225); however,

provides no evidence of local perceptual precedence supported by the ROI studied in either the non-inverted or inverted condition of the DFEP.

9.1 Introduction to Study 4

As previously discussed, categorical symptom-based methods of diagnosis were created to produce cut-offs and hence introduce discontinuity between individuals with autistic conditions and the general population. Recent population studies have introduced the notion that ASD diagnoses lie on a SCI severity continuum (78). Indeed, the previous study presented in this thesis supports that high functioning individuals with SCD who have, and those that do not have, a diagnosis of ASD have qualitatively similar SCI to that seen in autism. Therefore, quantification of SCI as a dimension of behaviour across ASD boundaries was undertaken to effect the informative inclusion of all individuals with SCI, as seen in autism, in this dimensional fMRI study.

Studies using the SRS have found sub-syndromal autistic impairments among siblings of probands with PDD (376). The expression of the broader phenotype in siblings has meant that they have not previously been utilised as controls in fMRI studies based on categorical diagnosis. Assuming the valid measurement of SCI in FDR using the SRS, siblings arguably represent an extremely informative group and a better control for non-genetic factors, such as shared environment, than non-related individuals. A recent study using the SRS to measure autistic symptoms in the male siblings of individuals with autism found that SCI was also optimally characterised along a single, heritable, continuous severity dimension in this group, similar to the finding in individuals with autism (398), supporting the use of the SRS in this group of FDR. The dimensionalisation of autistic symptomatology in affected individuals and their FDR allows for the informative inclusion of these individuals into aetiological studies of SCI. Quantification of autistic symptomatology also allows for investigation of correlations, as well as associations, between brain activation, cognitive performance and behavioural dimensions such as SCI and, allows the relationship between different potential levels of explanation for the SCI to be investigated. In addition to dimensionalisation of autistic symptoms, the use of cognitive and functional levels of explanation to constrain potential explanatory models reduces the behavioural heterogeneity that occurs when recruitment is based solely on diagnostic criteria. Modelling and quantifying continuously distributed characteristics in high functioning young men with SCD and their siblings represents a more powerful approach to identifying relationships between levels of explanation than diagnosis, as continuously distributed characteristics reflect the true state of nature better than the reductive dichotomy of 'affected' and 'non-affected' diagnostic status (326). Developing integrated research models, which inform the selection of more homogeneous groups for aetiological investigation, would ultimately positively impact on the power of fMRI studies to determine the neurobiology of SCI.

In terms of developing an integrated research model for SCI, previous fMRI research has focused on reduced right FG specialisation for face processing as a possible explanation for the SCI in ASD (6-8). Previous neuroimaging studies have implicated the right FG in configural processing of non-inverted face percepts (348) and the ITG in the feature-based processing of inverted face percepts in typically developing individuals (229). Reduced right FG activation has been reported during face processing in ASD and activation in the ITG implicated in the perceptual processing of non-inverted face percepts in

individuals with autism (18). These studies support that typically developing individuals are predisposed toward a more 'configural' style of visual processing supported in the right FG when presented with face percepts (217) and suggest that individuals with ASD may be predisposed toward a more 'detail' orientated style of visual processing supported in the ITG.

This perceptual style has also been reported in the fathers and male siblings of individuals with ASD (169, 181) suggesting that this perceptual style is familial, and therefore, would also, potentially, provide a genetically valid level of explanation in any model of SCI in ASD. This atypical perceptual style has been associated with face processing deficits (17) and may be related to a lack of expertise in configural processing and reduced expertise in the attribution of emotion in individuals with SCI. However, recent fMRI research using static face percepts has reported comparable right FG activation to typically developing individuals when individuals with ASD attended to the eyes region of the face (9) and during the viewing of faces of familiar people (10). Consequently, face processing deficits and the associated right FG hypo-activation hypothesis has become a contentious explanation for the SCI seen in autism. Another plausible explanation for SCI in ASD is reduced expertise in the attribution of emotion from facial expressions. Reduced expertise in the attribution of emotion secondary to reduced right FG specialisation for configural processing of dynamic facial expressions provides a plausible hypothesis for the SCI seen in ASD. Whilst this has been acknowledged as a potential explanation for the SCI seen in autism (1), there has actually been little integrated research investigating the relationship between SCI and the neural substrates of expertise in attribution of emotion from facial expressions (11). Reduced expertise in the attribution of emotion secondary to reduced right FG specialisation for configural processing of facial expressions are good candidates for the cognitive and functional levels of explanation respectively for SCI – the core deficit across all ASD diagnostic categories (1, 2).

9.2 Aims of Study 4

The main aim of the dimensional fMRI study presented in this thesis was to determine the relationship between SCI, expertise in the attribution of emotion and neural activation in the FG and ITG during emotion attribution from dynamic facial expressions in this group of high functioning individuals with SCI and their brothers.

9.3 Rationale of Study 4

The specific rationale pertaining to this study was that the dimensionalisation of autistic symptomatology, measurement of expertise in the attribution of emotion and quantification of the neural activation in the FG and ITG ROI during the attribution of emotion from dynamic facial expressions, would allow associations and correlations between the behavioural, cognitive and functional levels of explanation for SCI to be determined. Dimensionalisation of autistic symptomatology in the previous study demonstrated that diagnosis did not differentiate distinct SCI severity groups and supported the inclusion of individuals with SCI qualitatively similar to autism, but quantitatively insufficient to meet all domains for a diagnosis of autism, in the dimensional fMRI study. Non-inverted and inverted dynamic facial expressions were incorporated in the DFEP to allow interrogation of right FG specialisation for face processing and enhanced local perceptual precedence in individuals with SCI. Non-inverted dynamic facial expressions offered the opportunity investigate if reduced right FG

specialisation for configural processing is related to reduced expertise in the attribution of emotion offering a potential explanation for SCI in high functioning young men with SCD. Non-inverted dynamic facial expressions also offered the opportunity to determine if individuals with SCI demonstrate an enhanced local perceptual precedence for local feature-based processing based in the ITG ROI. The inverted condition of the DFEP was incorporated to tested the assumption that neither group would have expertise for the attribution of emotion from inverted facial expressions from inverted facial expressions. Specifically, both groups would have comparable levels of expertise and demonstrate comparable right FG activation during the attribution of emotion from inverted faces. The inverted condition of the DFEP also investigated for evidence of an enhanced local perceptual precedence for local feature-based processing of inverted faces based in the ITG ROI in these high functioning young men with SCD.

9.4 Hypothesis of Study 4

- Increased SCI would be related to reduced expertise in the attribution of emotion in the non-inverted condition of the DFEP if individuals with SCD have reduced right FG specialisation for configural processing of face precepts.
- Individuals with SCD would be less expert in the attribution of emotion associated with reduced right FG specialisation for the configural processing of faces in the non-inverted dynamic facial expressions condition of the DFEP.
- Individuals with SCD would demonstrate a local perceptual precedence associated with greater ITG ROI activation than their brothers in the non-inverted condition of the DFEP.
- SCI would be not be related to expertise in the attribution of emotion or right FG activation in the inverted condition of the DFEP.
- Individuals with SCD would have comparatively similar expertise and right FG activation to their brothers during the attribution of emotion if configural processing does not occur during the attribution of emotion from inverted dynamic facial expressions.
- Individuals with SCD would have greater ITG ROI activation if they exhibit an enhanced local perceptual precedence during the attribution of emotion from inverted facial expressions.

9.5 Methodology Specific to Study 4

To address the aims of this dimensional fMRI study, 60 probands with SCD and their FDR (n = 241) were recruited as previously described, and the SRS used to quantify SCI in all participants. For the dimensional fMRI study, 14 probands between the ages of 10-18 years, with and without a diagnosis each of autism whom had a brother within 4 years of age without a diagnosis, were recruited from the larger behavioural study. Of the 14 brother pairs,10 brother pairs also fulfilled the additional fMRI inclusion criteria and were recruited to participate in the dimensional fMRI study.

The dimensionalisation of autism symptomatology and the development of the DFEP offered an opportunity to obtain a greater insight into the perceptual style of individuals with SCI during dynamic facial expressions processing. The DFEP, which included non-inverted and inverted dynamic facial expressions conditions, was developed to address the configural and attentional limitations present in the paradigms used in the categorical fMRI studies. The DFEP represented a more naturalistic facial expression processing paradigm that require continuous attention to and/ or the configural processing of

dynamic developing facial expressions. The DFEP involved processing non-inverted and inverted dynamic facial expressions that became happy, sad or did not change in expression to ensure an explicit measure of task performance, but was developed to investigate the neural activation related to the perceptual processing while participants attributed emotion from dynamic facial expressions. Specifically, neural activation in the right FG known to be involved in the configural processing of non-inverted facial expressions in typically developing individuals (348), and neural activation in the ITG known to be involved in the feature-based perceptual processing of inverted facial expressions in typically developing individuals and non-inverted faces in autism (18) was measured.

The DFEP was presented using an event-related design in a 3T fMRI scanner to capture the activation related to emotion attribution from dynamic facial expressions in these hypothesis-driven FG and ITG ROI chosen *a priori*. During the experiment, accuracy and response time were recorded as measures of expertise in the attribution of emotion from dynamic facial expressions in both individuals with SCD and their brothers. ROI analysis was undertaken on fMRI data acquired while these high functioning young men attributed emotion from non-inverted and inverted dynamic facial expressions. The non-inverted verses the inverted condition of the DFEP, and the inverted verses the non-inverted condition of the DFEP, were contrasted to isolate activation associated with configural and feature-based processing respectively. Neural activation in the FG and ITG ROI was quantified for each of the contrasts to determine if activation in either of these two anatomical ROI related to SCI or expertise in emotion attribution from dynamic facial expressions in these high functioning young men with SCD and their brothers.

9.6 Results of Study 4

9.6.1 Behavioural Measure Results

9.6.1.1 FDR Recruited for Genetic Study

At the time of the fMRI, 60 families consisting of 241 individuals (60 mothers, 59 fathers, 60 probands, 35 brothers and 27 sisters) had been recruited and characterised as part of the ongoing genetic study of SCI at Stanford University. The ADI-R and SCQ status of the probands has been previously presented in Study 3. In this sample, the SRS score ($r = -0.321$, $p = 0.0001$) was indirectly correlated with age across relative groups, but not correlated with IQ. There was a significant difference between relative groups for the SRS score [$F(63, 177) = 158.4$; $p < 0.0001$; fixed factor family $p = 0.003$] and the proband group had a significantly higher score on the SRS than all other relative groups ($p < 0.0001$). The father group also had a significantly higher SRS score than the mother ($p < 0.0001$), male sibling ($p < 0.0001$) and female sibling ($p < 0.0001$) groups.

9.6.1.2 Probands and Brothers Recruited for the FMRI Study

From these sixty families, 10 probands with brothers within 4 years of age fulfilled criteria for inclusion in the fMRI study. Of these 10 probands, 6 fulfilled all ADI-R criteria for a diagnosis of autism and 4, who did not fulfil the cut-off for repetitive behaviours, did not fulfil ADI-R for a diagnosis of autism. Importantly, all probands and no brothers in the fMRI study were above threshold for a diagnosis of autism on the social impairment domain of the ADI-R.

The proband group had mean SRS score = 117 (SD = 17.9, range = 93-142) and mean SCQ score = 20 (SD = 6.8). The brother group had a mean SRS score = 15 (SD = 13.2; range = 0-47) and mean SCQ score = 3 (SD = 3.7). There was no correlation between age or IQ and the SRS score. There was a significant difference in SRS score [$t(18) = 238$, $p = 0.001$] and SCQ score [$t(18) = 6.91$, $p = 0.0001$] between the proband and brother groups.

9.6.2 Demographic and Neuropsychological Results

9.6.2.1 Proband and FDR Recruited for Genetic Study

The ethnicity and socioeconomic status of the families from which the probands for the fMRI study were recruited and the clinical and medication status of the larger sample of probands are given in Study 3. The age, FSIQ and SRS scores for each of the FDR groups are given in the following table (Table 9-1).

Table 9-1 Age, FSIQ and SRS scores for Proband and Relative Groups

Relative Groups	N	Age (mean)	Age (SD)	FSIQ (mean)	FSIQ (SD)	SRS (Range)	SRS (Mean)	SRS (SD)
Mother	60	45.1	4.4	125	10.2	0-93	27.18	17.8
Father	59	46.9	5.2	126	11.3	6-146	41.98	30.3
Proband	60	13.5	2.5	123	15.5	67-145	105.78	18.8
Male Sibling	35	13.3	3.6	126	12.5	0-121	22.06	22.6
Female Sibling	27	13.9	3.9	119	13.1	3-73	18.78	14.3

Table 9-1 presents the age and IQ of the proband and their first-degree relatives

There was a significant difference in age between FDR groups [$F(1, 240) = 969$, $p < 0.001$]. Specifically, parent-parent ($p < 0.018$), parent–proband ($p = 0.0001$), parent–female sibling ($p = 0.0001$) and parent -male sibling ($p = 0.0001$) groups were significantly different in age. However, proband -male sibling ($p < 0.860$) and proband–female sibling ($p < 0.626$) groups were not significantly different in age.

There was a trend toward a significant difference between FDR in mean FSIQ [$F(63, 176) = 2.403$; $p = 0.052$]. Although FDR were not significantly different on VIQ [$F(63, 176) = 1.770$; $p = 1.37$], there was a significant difference in PIQ [$F(63, 176) = 4.50$; $p = 0.002$] between relative groups. The father and proband groups had significantly different PIQ ($p = 0.001$) and there was a trend towards a significant difference in PIQ between the mother and proband groups ($p = 0.068$). The mother, father, proband, brother and sister groups all had average to above average cognitive function.

9.6.2.2 Probands and Brother Groups for the FMRI Study

The proband and brother group comprised of 9 Caucasian brother pairs and 1 Asian brother pair. There was no significant difference in the socio-economic status between groups as both brothers were from the

same family. All probands had a clinical diagnosis: 7 probands had a diagnosis of AS; 1 proband had a diagnosis of PDD-NOS; 1 proband had a diagnosis of NLD; and, 1 proband had a diagnosis of HFA. There were 6 probands who were receiving serotonin reuptake inhibitors; 2 probands receiving gabapentin; and, 2 probands who were not receiving any medication in the SCD group. No brothers had a clinical diagnosis or were receiving any of the afore mentioned medications.

There was no significant difference in the age [$t(18) = 0.835$, $p = 0.415$] between the proband (mean age = 14.8, SD = 2.09, range = 11-19 years) and the brother (mean age = 13.8, SD = 3.32, range 10-18 years) groups. There was no difference in intelligence [FSIQ: $t(18) = 0.541$, $p = 0.595$; VIQ: $t(18) = 0.313$, $p = 0.758$; PIQ: $t(18) = 0.478$, $p = 0.638$] between the groups. The proband group [FSIQ = 131, SD = 14.7; VIQ =133, SD = 17.5; PIQ = 121, SD =10.47] and the brother group [FSIQ = 128, SD = 12.7; VIQ = 131, SD = 16.8; PIQ = 119, SD = 11.0] had average to above average cognitive function. The proband and brother groups were right-handed as assessed by the EHI (293) and there was no significant difference in handedness between the proband and brother groups [$t(18) = 0.800$, $p = 0.434$; proband group RH = 84%, SD = 17.0; brother group RH = 74%, SD = 15.3]

Non-inverted DFEP percentage correct was correlated with SRS score ($r = 0.523$, $p = 0.018$) and age ($r = 0.603$, $p = 0.005$), but not IQ. The SRS score was still correlated with non-inverted DFEP percentage correct ($r = 0.558$, $p = 0.013$) after accounting for age. There was no significant difference in non-inverted DFEP percentage correct between the proband group and brother group [$F(1, 19) = 0.001$, $p = 0.992$; proband group percentage correct = 81%, SE = 2.8, range = 74-87; brother group percentage correct = 80%, SE = 2.8, range = 74-87]. There was a trend toward a significant difference in non-inverted DFEP response time between the proband and brother group [$F(1, 19) = 4.76$, $p = 0.066$; proband response time = 5534 msec, SE = 244 msec, range = 4958-6111 msec; brother group response time = 4746 msec, SE = 244 msec; range = 4170-5323 msec].

Inverted DFEP percentage correct was correlated with age ($r = 0.545$, $p = 0.013$), but not SRS or IQ. There was a trend in the inverted condition of the DFEP towards response time being correlated with SRS score ($r = 0.414$, $p = 0.07$), but not age or IQ. There was no significant difference in inverted DFEP percentage correct [$F(1, 19) = 0.842$, $p = 0.386$; proband percentage correct = 67%, SE = 3.8, range = 58-76; brother percentage correct = 72%, SE = 3.8, range = 63-81] or response time between the proband and brother group [$F(1, 19) = 2.77$, $p = 0.140$; proband response time = 5754 msec, SE = 201, range = 5278-6220; brother group response time = 5256 msec, SE = 201, range = 4781-5732 msec].

9.6.3 Regions of Interest Analysis Results

9.6.3.1 Non-inverted Dynamic Facial Expression Paradigm

Right FG activation in the non-inverted condition of the DFEP was correlated with SRS score ($r = 0.46$, $p = 0.041$) and indirectly correlated with age ($r = -0.520$, $p = 0.019$) in the non-inverted condition of the DFEP across both groups. However, there were no correlations with DFEP percentage correct or response time and the other ROI for the non-inverted condition of the DFEP.

There was a significant difference in average right FG activation between groups [F(1, 19) = 5.1, p = 0.05]. Specifically, the proband group (mean = 0.509, SD = 0.12) had significantly more average right FG activation than the brother group (mean = 0.377, SD = 0.12) after co-varying for age in the non-inverted condition of the DFEP. There was no significant difference in average activation between groups for the left FG and ITG in the DFEP.

9.6.3.2 Inverted Dynamic Facial Expression Paradigm

The average right FG activation was indirectly correlated with the SRS score (r = -0.597, p = 0.005) in the inverted condition of the DFEP. The right average ITG activation was indirectly correlated with the response time (r = -0.519, p = 0.019) in the DFEP inverted condition of the DFEP.

Between groups there was a significant difference in average right FG activation in the inverted condition of the DFEP [F(1, 19) = 10.16, p = 0.011]. Specifically, the proband group (mean = 0.288, SD = 0.15) had less average right FG activation than the brother group (mean = 0.538, SD = 0.15) in the inverted condition of the DFEP. There was no significant difference in average activation between groups in the left FG or ITG in the inverted condition of the DFEP.

9.7 Data Interpretation 4

As part of a genetic study of SCI in ASD, further discussion of which is beyond the scope of this thesis, SCI was measured as a dimension of behaviour in 60 high functioning young men with SCD and their 241 FDR. The quantification of autistic symptomatology confirmed that the proband group had significantly greater SCI than all of their FDR groups. Interestingly, the father group also had significantly greater SCI than mother, male and female sibling groups. This is in keeping with reports of the expression of the BAP in the parents of individuals with ASD (399) and the higher prevalence of autistic symptoms in males (80), and demonstrates the utility of quantifying SCI in FDR of these high functioning individuals.

In the dimensional fMRI study, young men with SCD with brothers within four years of age were recruited. The brothers were recruited as controls to facilitate matching for IQ and socio-demographic factors in these high functioning individuals with SCD. Brother pairs within 4 years were used to minimise the confounding effects of age differences on brain activation comparisons. The variables of interest, such as SCI, were measured in both the proband and the brother group. Although, the brother group may express aspects of the broader phenotype not measured in the study, as these were not variables of interest, the brothers represented a more stringent control group than unrelated individuals. Although brother pairs could not be age-matched, there was no significant difference in average age or intelligence between the proband and brother groups. By virtue of their age (10 - 19 years) and average to high cognitive ability, these high functioning young men with SCD and their brothers were able to give informed consent, understand instructions and perform the DFEP in the scanner environment.

Previous studies looking at SCI have focused on low functioning individuals from particular ASD diagnostic groups such as autism (391). However, SCI represents the core deficit across all of the ASD diagnostic categories (1, 2) and many individuals with such SCI are high functioning (400). The use of

categorical diagnostic groups, such as autism, has limited attempts to relate dimensions of behaviour to cognitive strategy and brain function in ASD. Therefore, 10 high functioning young men with SCI as seen in autism, each with a brother within four years of age, were recruited for the fMRI study whether they attracted an ASD diagnosis or not. Of these 10 high functioning individuals with SCD, 6 fulfilled all ADI-R criteria for a diagnosis of autism and 4 did not fulfil criteria of an ADI-R diagnosis of autism because they were not above threshold on the repetitive behaviours domain of the ADI-R. However, all high functioning young men with SCD fulfilled the social impairment domain for an ADI-R diagnosis of autism. Recent studies have called for revision of the ADI-R to include the diagnosis of PDD-NOS (401) and improve sensitivity for individuals with SCI who do not fulfil a diagnosis of autism. However, the ADI-R was not intended to quantify autistic symptomatology and such an improvement in sensitivity would not address the limitations imposed on aetiological studies by the continued use of categorical classification. In this study the SRS, which has recently become generally available, was used to measure SCI as a dimension of behaviour and quantify autistic social symptomatology to circumvent these limitations. The SRS scores indicated that all high functioning young men had quantitatively and qualitatively similar SCI to that previously reported for PDD-NOS (13) and the individuals, who did not fulfil ADI-R criteria for autism in this study, would have fulfilled a diagnosis of PDD-NOS.

The SRS scores for the high functioning young men and brother groups were distributed across the range of the instrument allowing for correlation. As there was no overlap in SRS scores between the high functioning young men and brother groups, the groups were also considered dichotomous and comparison between the groups undertaken. The use of the SRS to dimensionalise autistic symptomatology identified that these high functioning young men with SCD had significantly greater SRS scores than their brothers confirming significantly greater autistic symptomatology in the proband than the brother group. The recruitment of brothers provided the optimal control for shared environment and, potentially, resulted in greater variance in SRS score than if non-related individuals had been recruited, allowing for correlation analysis to be undertaken.

In the dimensional study, there was no relationship between intelligence and SRS score within or across groups in accordance with previous reports (13). Contrary to previous studies in which the SRS score was correlated with age, there was no correlation with age in this study (22). This may be reflective of the narrow age range, which may have been insufficiently broad to identify a relationship between age and SRS score, in those recruited for this fMRI study. An alternative explanation may be the older age range in this study, which may have included a narrower developmental range and have reduced the likelihood of identifying any relationship between age and SRS score in this fMRI study.

The SRS score was directly correlated with accuracy, but not response time, across both groups in the non-inverted condition of the DFEP. Therefore, contrary to our hypothesis that SCI would be related to reduced expertise in the attribution of emotion, those with the greatest SCI were actually the most accurate in the attribution of emotion from non-inverted facial expressions. Although, the groups were as accurate, there was a trend ($p = 0.066$) toward a significantly slower response time in the proband group compared to the brother group. Possible reasons for this unexpected relationship between accuracy and autistic symptomatology across the groups include individuals with SCI actually being more accurate in

the attribution of emotion from dynamic facial expressions; however, the trend toward significantly greater response time in the SCD group does not fit with this. Another possible reason is that individuals with SCI adopt a speed/ accuracy trade-off strategy and respond later in the paradigm when the dynamic facial expression is more developed. The similar accuracy and trend toward significantly greater response time in the SCD group would potentially fit with this explanation. Response time was not correlated with accuracy and was related to different stages in the development of the dynamic facial expressions, therefore, it was inappropriate to co-vary to determine the effect of response time in this study. The trend toward a significantly slower response time in the proband group compared to the brother group is in keeping with the adoption of a non-linear speed/ accuracy trade-off strategy. The trend toward a significantly increased response time in the proband group may also be related to the need to recruit greater right FG to perform comparable configural process to the typically developing group in the non-inverted condition of the DFEP. The longer response time may reflect the need for greater attention to the developing facial expression and greater attention to the facial expressions would also fit with the right FG hyper-responsiveness in the proband group in this study. Alternatively, the trend toward a significantly increased response time in the proband group may be related to the use of a slower visual strategy and/ or slower motor response during the non-inverted condition of the DFEP.

In the non-inverted condition of the DFEP, the right FG activation was indirectly correlated with age indicating that the younger individuals in this study had the greatest right FG activation during the attribution of emotion from non-inverted dynamic facial expressions. A recent developmental study of right FG activation, which compared processing of face percepts with the processing of house percepts, reported a direct correlation between right FG activation and age in typical developing individuals providing evidence that involvement of the right FG in face processing develops with age in typically developing individuals (348). The indirect relationship between age and right FG activation in this study suggests that the involvement of the right FG in face processing is not increasing with age in young men with SCD and their brothers. This may reflect reduced specialisation for configural processing in the right FG in these related individuals whom may all have a genetic predisposition toward atypical visual processing of face percepts. There are, however, no developmental studies of right FG activation using dynamic face processing tasks in high functioning individuals with SCD and their FDR, both of whom may also have a genetic predisposition toward atypical visual processing of face percepts. Possible explanations for the indirect relationship between age and right FG across groups include: the use of greater right FG activation during the processing of faces in younger individuals; the inclusion of brothers that may have a qualitatively similar but quantitatively less severe, atypical visual strategy; and, reduced attention to face percepts during the attribution of emotion from dynamic facial expressions in older individuals mediating reduced right FG activation as previously reported (9). Right FG activation was also directly correlated with SRS score across groups, after accounting for age, providing evidence that right FG activation increases with greater autistic symptomatology in these high functioning young men. Autistic symptomatology, measured using the SRS, has previously been reported to be greater in younger age groups (14). Both these correlations support the direct relationship between right FG activation and SCI in the individuals in this study. A previous study, in which lower functioning individuals with ASD viewed faces, reported an indirect correlation between right FG activation and the

social impairment domain score of the ADI-R in autism. Although, the ADI-R was not designed to quantify autistic symptoms, calling into question the validity of using the social impairment domain of the ADI-R for correlation analysis, the proposal made in this study may offer explanation for the hyper-responsiveness in the non-inverted condition of the DFEP. The authors proposed that hypo-activation of the right FG in these individuals with autism was related to decreased attention to the eyes region of the face to reduce the autonomic over-arousal experienced by individuals with ASD while viewing faces (203). This proposal presumably means that if these individuals with autism attended to faces then they would not exhibit right FG hypo-activation and, potentially, those that fixated for longer on the face, to attribute emotion for example, would actually demonstrate increased right FG activation. This would be in keeping with the trend towards an increased response time and increased right FG activation in the SCD group in this study.

The high functioning individuals with SCD in Study 4 were as accurate as their brothers. In effect the comparative accuracy in the non-inverted condition of the DFEP indicates that both groups are able to perform the task and facilitates comparison of brain activation between groups (39). There was a trend toward a significantly greater response time in the proband group compared to the brother group, which provides evidence that the proband group did not avert their gaze as seen in the previous study and suggests that the right FG hyper-responsiveness may be related to the longer attention to the dynamic facial expression in the non-inverted condition of the DFEP, which was designed to necessitate configural processing for its successful completion.

Between group ROI analysis found that to achieve comparable performance the proband group activated the right FG significantly more than the brother group in the non-inverted condition of the DFEP, indicating that individuals with SCD used greater right FG than their brothers during the perceptual processing of non-inverted dynamic facial expressions. Previous studies have reported reduced right FG in lower functioning individuals with autism, associated with reduced capacity to perform the task and proposed reduced configural processing in ASD (6, 18). However, it is difficult to determine if brain activation is related to the CCI when there are also differences in task performance. It is necessary to study groups while undertaking tasks they are both able to perform to compare brain activation in fMRI experiments (39). Recent studies have reported comparable right FG activation when individuals with autism processed familiar faces (10) and when individuals with autism attended to a cross placed in the centre of presented face percepts (9). The findings of these more recent studies support that the right FG is specialised for the configural processing of face percepts and not functionally impaired in autism. A recent study presented primary emotions at varying emotional intensities to individuals with AS and reported that both the individuals with AS and the typically developing controls activated significantly increased right FG in response to increasing intensities of emotion during the neutral implicit face processing task. The AS group was reported to demonstrate hypo-responsiveness compared to the typically developing group overall in this study. However, as this study presented an implicit face processing task that had no explicit measure of performance, it remains unclear if the differences in FG activation are related to attentional differences, differences in the visual processing of face percepts in individuals with ASD and/ or other differences in task performance. The right FG has also been reported

to be correlated with the configural processing of dynamic facial expressions (261), therefore, increased right FG could be expected in relation to increased configural processing, but could also be related to increased intensity of attention/ length of attention allocated to developing facial expressions in the individuals with the greatest SCI (9). Attention allocation to different aspects of the face has been reported as both atypical (316) and typical (402) in autism, as has configural processing, and the characteristics of both these constructs as defined in the literature appear to be overlapping and inter-dependant. Future studies are required to tease attention and configural processing apart and determine the underlying explanation for right FG hyper-responsiveness in high functioning young men with SCD in this condition of the DFEP.

The left FG and the ITG had both been reported to be involved in the visual processing of detail in faces. The left FG has been previously reported to be involved in the feature-based analysis of faces in typically developing individuals (235). The ITG has also been reported as involved in the feature-based visual processing of objects in typically developing individuals and to be activated during the processing of faces in individuals with autism (18). However, there was no significant activation difference between groups for the left FG or either left or right ITG ROI in the non-inverted condition of the DFEP. Therefore, there is no evidence for enhanced local perceptual processing of faces during the attribution of emotion from non-inverted dynamic facial expressions based on the ROI studied in these young men with SCD when compared with their brothers. Of course, enhanced local perceptual processing of faces supported by brain regions, other than those ROI in this study could explain the comparable performance between groups, and this needs to be further investigated.

In the inverted condition of the DFEP, accuracy was correlated with age, but not SRS score or IQ. The SRS score did not predict age, IQ or accuracy in the attribution of emotion from dynamic facial expressions, but did predict right FG activation. The average right FG activation was indirectly correlated with the SRS score in the inverted condition of the DFEP indicating that autistic symptomatology was indirectly associated with right FG activation during the attribution of emotion from inverted dynamic facial expressions. This finding, in conjunction with comparable accuracy, provides evidence for a relationship between reduced right FG activation and SCI when the task can be completed successfully without configural processing. There was trend towards inverted DFEP response time being directly correlated with SRS score, inferring that those with the greatest autistic symptomatology are the slowest at attributing emotion from inverted facial expressions. The use of an atypical perceptual processing strategy, supported by the right ITG, during the attribution of emotion from inverted dynamic facial expressions offers a possible explanation for the relationship between SRS score and response time in the inverted condition of the DFEP.

There was no significant difference in inverted DFEP accuracy between the proband and the brother group implying that both groups could perform the condition and facilitating the comparison of brain activations during inverted condition of the DFEP. The lack of significant difference in accuracy and response time provides evidence that individuals with SCD have comparable expertise in the inverted condition of the DFEP as predicted. However, contrary to the study hypothesis, which predicted comparable right FG activation, the proband group had lower average right FG activation than the

brother group in the inverted condition of the DFEP. Possible explanations for the proband group activating significantly less right FG activation than their brothers when attributing emotion from inverted dynamic facial expressions include: decreased innate predisposition to attend to inverted faces or a decrease innate predisposition to configurally process inverted faces in the SCD group. However, a greater innate predisposition to attend to inverted faces or configurally process inverted faces in the brother group. The right FG hypo-activation in the socially impaired group suggests that they are not innately predisposed to process inverted faces configurally. In contrast their socially unimpaired brothers activated the right FG significantly more and apparently attempted to continue to configurally process the inverted facial expressions. This drive toward configural processing of inverted faces has previously been reported in typically developing individuals (403). Individuals with SCD and their brothers had comparable ITG activation, reflecting the comparable use of feature-based processing supported in the ITG in the inverted condition of the DFEP in both groups. However, the indirect relationship between right ITG activation and response time in the inverted condition of the DFEP suggests that feature-based processing is still a slower visual strategy when processing inverted facial expressions across groups.

9.8 Key Findings of Study 4

The quantification of autistic symptomatology confirmed that the probands had significantly greater SCI than all of their FDR. Interestingly, fathers also had significantly greater SCI than mothers, male and female siblings. The fMRI studied a subset of 10 high functioning young men with SCD, who had brothers within 4 years of age, attributing emotion from non-inverted and inverted developing dynamic facial expressions. Contrary to the hypothesis, the key findings from the non-inverted condition of the DFEP were that the SRS score was directly correlated with accuracy and right FG activation during the attribution of emotion from non-inverted dynamic facial expressions. Individuals with SCD were as accurate as their brothers, but showed a trend towards significantly increased response time, and activated significantly greater right FG activation than the brother group when attributing emotion from non-inverted dynamic facial expressions. The relationship between right FG activation and SRS score supports that those with the greatest autistic symptomatology actually activate the greatest right FG in response to non-inverted dynamic facial expressions. The significantly greater FG activation in the proband group in the non-inverted condition provides evidence for right FG specialisation for the configural processing of faces in individuals with SCD. This right FG hyper-responsiveness may relate to the inherent need for attention to the whole face during the DFEP and/ or the need for configural processing throughout the non-inverted task.

The key findings of the inverted condition of the DFEP are that the SRS score did not predict accuracy or response time, but was indirectly correlated with right FG activation across groups. Response time was indirectly correlated to right ITG activation in the inverted condition across groups, so those with the greatest ITG activation were slowest in the attribution of emotion from inverted facial expressions. In support of the hypothesis that both groups would have comparable expertise, individuals with SCD had comparable accuracy, response time and ITG activation as their brothers; however, they activated significantly less right FG activation when attributing emotion from inverted dynamic facial expressions. This provides evidence that the individuals with SCD did not use a configural processing strategy in the

inverted task, despite the continued use of right FG dependent strategies in the brother group and lack of evidence for local perceptual precedence in the ROI studied.

9.9 Methodological Considerations of Study 4

The following methodological issues with respect to subject recruitment, behavioural measures, paradigm design and procedure, image pre-processing and ROI processing need to be taken into account when considering the findings of this study.

9.9.1 Subject Recruitment

Previous studies of face processing in ASD have reported with sample sizes of less than ten participants (18). Although, relatively speaking the sample size used in this study was not that small, the power of the study to detect significant correlations and differences between groups would have been improved by recruitment of a larger sample. The lack of correlation between expertise in the attribution of emotion and SCI may have been attributable to the sample size, as may the trends that did not reach significance. Future studies require to recruit larger sample sizes and determine if correlations and significant difference exist between groups in these larger samples. Consideration of sample size is of particular relevance in interpretation of the null findings for ITG and left FG regions in group comparisons.

Future fMRI studies that exclude individuals receiving medication require to replicate the findings of this study. Replication studies should also include females and lower functioning individuals with SRS to determine if the findings of this study can be generalised across different populations with SCD. The use of relatives (brothers) as the control group addressed the research question and provided the optimal control for environmental factors in this study; however, the lack of an unrelated control group means that the results from this study sample cannot be generalised to unrelated individuals with SCD in the general population. The variance in SCI may have been affected by using brother pairs; however, it is likely that the variance in SRS score was increased using this sample allowing correlations between SCI and performance on the DFEP to be investigated. The use of relative groups also introduces a 'family effect', which was modelled to determine the variance attributable to relative group. Future studies with non-related controls are needed: to determine the actual family effect; determine the prevalence of autistic traits in the relatives of individuals with SCD; and, to allow the calculation of relative risk for SCD in the general population.

The study of siblings is potentially more informative for genetic studies as they share, on average, 50% of their genes and offer a control for shared environment. If the siblings are approximately of the same age, a paired design increases the power of the study to detect variance attributable to the variable of interest. However, it is not possible to precisely age match the siblings with their respective proband in a sib-pair design. In comparison, non-related control groups can be gender, age, sex and IQ matched with individuals with SCI. However, recruitment of non-related controls is difficult and introduces inefficiency in terms of ascertainment. Non-related controls are often not as invested in the research and, therefore, are less likely to participate without financial inducement/ recompense for their time. In contrast, related individuals are keen to participate, and often prepared to participate without financial inducement/ recompense for their time because they are invested in the research. The recruitment and re-

imbursement of non-related controls was not possible within the financial constraints of this study and although the recruitment of non-related controls was attempted the attempt was not successful without recourse to re-imbursement.

In autism and related conditions siblings are known to express the broader phenotype and the recruitment of the siblings of young men with SCD resulted in the inclusion of siblings with a range of social communication expertise. However, the quantification of SCI resulted in individual probands and siblings remaining informative and allowed for correlation analysis. The use of probands and their brothers provided greater variance and allowed the relationship between behavioural, cognitive and functional variables to be studied in individuals with SCI. However, without replication in non-related groups already ascertained from epidemiological representative samples, then the relationship between the variables cannot be generalised to the wider population.

9.9.2 Behavioural Measures

Many of the issues discussed in Study 3 are relevant to Study 4. In addition, and of relevance to this study, the SRS has not previously been reported to represent a biologically valid dimension of behaviour. Although this study demonstrated indirect and direct correlations between SRS score and right FG activation during the attribution of emotion in the non-inverted and inverted condition of the DFEP respectively, correlation does not mean causation. In the future techniques such as transcranial magnetic stimulation will provide evidence to support or dispute such a causative relationship between the right FG and autistic symptomatology measured using the SRS.

9.9.3 Paradigm Design and Procedure

The previous categorical studies focusing on ASD presented in this thesis provided evidence to support that high functioning individuals with ASD can attribute emotion from facial expressions, but suggest that this is task-dependant (296). Consideration of the characteristics of the tasks used in Studies 1 and 2 suggests that one possible explanation for this finding is that individuals with ASD have a predisposition to atypically process face percepts, and only typically process face percepts in tasks that necessitate configural processing for their successful completion. The DFEP was designed on the premise that non-inverted dynamic facial expressions would require configural processing and the inverted dynamic facial expressions would not require configural processing; however, without objective measurement configural processing can be only be assumed not asserted. The DFEP represented an explicit emotion attribution task and was designed to require continuous attention and configural processing to attribute the correct emotion from the facial expression. Objective measurement of visual processing style and attention, such as eye-tracking technology, would have been optimal in this study. Eye-tracking technology can be used to determine the visual fixation profile of each individual participant and the average visual fixation profile across groups. Eye-tracking technologies allow percentage and period fixations to be determined and would have confirmed if both groups attended to the eye region of the face for comparable periods and identified visual fixation patterns. Eye-tracking technologies are necessary to determine if groups are using the same or different visual style and fMRI is necessary to determine the brain regions that support any visual style. In atypical development, it is possible that typical performance could be achieved using an atypical visual style supported outside the right FG by another regional of the brain.

However, it is also possible that another regional of the brain could be utilised, which has undergone functional adaptation, to perform 'configural' perceptual processing similar to that undertaken by the right FG in the typically developing brain.

The development of eye-tracking technology would have allowed objective behavioural measurements and task specific brain activation to be related to each other within the scanner. Unfortunately, eye-tracking technologies were not available in the fMRI environment at Stanford University when this study was undertaken. Eye-tracking should be incorporated into future studies to provide objective evidence of perceptual style and facilitate consideration of alternative explanations for the brain activations seen in this study. For example, the increased right FG activation during the non-inverted condition of the DFEP could have been due to: increased attention to the face percept; increased eye fixation; and/ or, facilitation of configural processing secondary to presentation of dynamic facial expression stimuli. Eye-tracking technologies would have allowed further interrogation and, ultimately, would have provided evidence to refute explanations that could not logically be assimilated with the fixation and fMRI data.

Future studies also need to perform psychometric analysis to better understand the trade-off between accuracy and response time in neurocognitive tasks. Participants can obviously be more accurate by responding more slowly, and can respond more quickly by being less accurate. Speed/ accuracy decisions are also influenced, and have been shown to be determined in part, by the strategic inclinations of participants as opposed to a built-in trade-off (291). Studies are also needed to determine if a composite neurocognitive measure such as expertise, which takes account of this trade-off, have utility. The lack of a single composite construct quantifying expertise, that takes accuracy and response time trade-offs into account, makes it difficult to correlate the behavioural and cognitive levels of explanation for SCI in these high functioning individuals and their brothers. Larger studies should be undertaken to determine if accuracy and response time do represent different cognitive or functional strategies, as suggested recently in fMRI vision research (301) and, therefore, need to be analysed separately as presented in this study.

Investigation of the variance in performance related to accuracy and response time needs to be undertaken in a larger sample of young men with SCD to determine if expertise could be represented by a composite variable. The variance in the performance was possibly reduced by the use of a 'practice' version of the DFEP, and previous exposure to a version of the DFEP as part of the larger behavioural study. Individuals with developmental abnormalities may be able to acquire skills through practice leading to intra-task variation (404). There is an argument for allowing participants to practice a task until both groups are at a similar level of performance before comparing neural activations (39). In the past, this has been considered erroneous and referred to as a practice effect or error; however, this determination depends on the research question. The variability in the performance would also have been reduced by the fMRI investigation of a much smaller sample and may have had an effect on this studies ability to find correlations between the behavioural, cognitive and functional levels of explanation.

All fMRI experiments in this thesis are based on the assumption of cognitive subtraction (405), and it is assumed that the subtraction of the control task from the experiment task isolates the activation associated with the CCI. However, this interpretation relies on two assumptions. The first assumption is that there will be more neuronal activity in a functionally specialised area when a task demands the explicit involvement of that area than when it does not explicitly involve that area. The second assumption is that of "pure insertion," which assumes that an extra cognitive component can be 'purely' inserted without affecting the expression of pre-existing components (406). This second assumption implies that the activations associated with the comparison of two tasks only reflect the cognitive component added in the activation task, leaving unchanged the components shared by activation and baseline tasks. Although there are many fMRI experiments based on cognitive subtraction, it is unlikely that cognitive constructs can be subtracted in this simplistic manner (407). Future studies using analysis such as conjunction and parametric analysis that do not rely on these assumptions are required.

9.9.4 Image Pre-processing

Future studies should use a rapid event-related experimental design and the GLM to determine the activation for each stimulus from overlapping neural activations as this will maximise SNR. The paradigm should be presented in a rapid event-related design, the presentation of stimuli counterbalanced (pseudo-randomised) and the ISI alternated or 'jittered' in a counterbalanced sequence. If these presentation conditions are met, the GLM can be used to determine the neural activation associated with each stimulus, despite the rapid presentation of stimuli resulting in overlapping neural activations. Studies have shown that the presentation of the stimuli or 'events' less than two seconds apart appears to fulfil the assumptions of linearity allowing for analysis within the framework of the GLM. This means that despite presenting overlapping events the activation for each individual event can be parsed-out. Rapid event-related fMRI provides a powerful means of mapping brain function in studies of primary cognitive process such vision (408). However, although these findings appear to hold for higher cognitive processes (409), in certain studies, non-linearities have been found to be quite pronounced (313). Future studies should investigate the use of rapid ER-fMRI to improve the SNR in studies of social communication and determine if non-linearity is an issue for individual events that are of prolonged presentation.

9.9.5 Region of Interest Processing

In all the fMRI studies in this thesis anatomical ROI were used; however, ROI can also be defined functionally from WBA maps for each prescribed paradigm. Functional masks, developed in a second matched control group, would determine the functional activation difference between experiment and control groups in the whole brain, while not relying on normalised brain anatomy. Functional activation 'masks' can be created using SPM99 software (410). However, to prevent confounds, the mask ideally requires to be obtained from a second 'equivalent' group of individuals, or used to quantify whole brain functional activation of the same group of individuals undertaking a different experimental condition. This technique, although functionally driven, is often not expedient as individuals, who could otherwise be eligible for the experimental group, are used to create the functional mask. Activation defined using functional masks is difficult to compare with findings from structural studies and difficult to compare

across functional studies. In summary, in contrast to WBA, which identifies qualitative differences in brain activation between specific groups with respect to a specific task, anatomical ROI quantify brain activation in regions defined anatomically, and are often determined from the literature. Functional ROI quantify differences in brain activation defined functionally and are specific to the group from which the mask is created and may be more appropriate in neurodevelopmental disorder populations.

9.9.6 Statistical Analysis

In this study, the probands and the sibling groups were not independent samples, therefore, a mixed model approach, which accounted for the variance attributable to being in the same family group, was necessary. Autistic symptomatology was measured dimensionally in siblings to determine if they expressed a broader phenotype below threshold for PDD-NOS. Then two distinct study groups were created using diagnostic instruments based on diagnostic cut-offs and group comparisons performed. The main value of quantifying autistic symptoms in siblings and probands in this study was that this enables the subsequent use of correlation analysis. The use of a quantitative, rather than qualitative, measure means that individual data points remain informative and correlation analysis, which is more statistically powerful, can be undertaken.

9.10 Conclusions and Implications of Study 4

The dimensional fMRI study found that SCI was directly related to accuracy, a proxy measure of expertise, during the attribution of emotion from non-inverted facial expressions. However, at a group level, individuals with SCD were actually as accurate in the attribution of emotion from non-inverted facial expressions, but demonstrated a trend toward increased response time. Therefore, this counter-intuitive finding in support of greater accuracy in the most socially impaired individuals would appear related to the fact that they are responding later in the development of the dynamic facial expression and provide partial support for a speed-accuracy trade-off. Although reduced expertise in the attribution of emotion from dynamic facial expressions was not statistically supported as a cognitive explanation for SCI in this dimensional fMRI study, the trend towards increased response time in the proband group supports the need for larger studies to determine if expertise in the attribution of emotion from non-inverted facial expressions is reduced in SCI.

Interestingly SCI, which was directly related to accuracy, was also directly related to right FG activation in the non-inverted condition of the DFEP supporting that the most socially impaired require to activate the greatest right FG activation during the processing of non-inverted facial expressions. This was associated with a statistically greater right FG activation in the proband group in the non-inverted dynamic facial expressions condition of the DFEP providing evidence of a right FG role in the attribution of emotion from dynamic facial expressions. However, contrary to the hypothesis, individuals with SCD had comparable ITG ROI activation as their brothers in the non-inverted condition of the DFEP and did not demonstrate a local perceptual precedence in the non-inverted condition of the DFEP.

There was a trend toward an indirect relationship between SCI and response time, the other proxy measure of expertise, during the attribution of emotion from inverted facial expressions and larger studies are necessary to determine if greater SCI does result in a faster response in the inverted condition.

However, accuracy and response time and, therefore, expertise were comparable between groups in the inverted facial expression condition of the DFEP. There was also a statistically significant indirect relationship between SCI and right FG activation in the inverted condition of the DFEP supporting that the most socially impaired had the least right FG activation in the inverted condition of the DFET. Individuals with SCD had reduced right FG activation in the inverted condition of the DFEP providing evidence that the comparable performance was associated with significantly less right FG activation the proband group and that both groups used comparable ITG ROI activation to support the feature-based perceptual processing of inverted facial expressions.

In summary, autistic symptomatology was found to be directly related to accuracy in the attribution of emotion from non-inverted dynamic facial expressions, and there was a trend toward an indirect relationship with response time during the attribution of emotion from inverted dynamic facial expressions. As accuracy and response time were measured as proxies for expertise, these findings would seem to indicate a relationship between SCI and expertise in the attribution of emotion. However, strategies such as accuracy-response time trade-offs need to be better understood and methods developed to prevent, account for and/ or measure expertise in a way that incorporates both accuracy and response time developed to allow for a better understanding of the relationship between the behavioural and cognitive levels of explanation for SCI. The direction of the relationship between right FG activation and SCI in the inverted and non-inverted conditions of the DFEP, although unexpected, is consistent with individuals with SCI activating greater right FG when the condition (non-inverted dynamic facial expression) requires configural processing and less right FG when the condition (inverted dynamic facial expressions) does not require configural processing for its successful performance. The different right FG activations patterns in the two conditions of the DFEP provide further evidence that activation in the right FG during the attribution of emotion from dynamic facial expressions is condition-dependant or task-dependant as previously reported in the categorical studies. In the non-inverted condition of the DFEP, which necessitated configural processing, high functioning young men with SCD activated the right FG significantly more than their brothers. This significantly greater activation provides evidence for right FG specialisation for the configural processing of facial expressions in these young men with SCD. Contrary to the right FG hypo-responsiveness findings of earlier studies (6, 18), the finding of right FG hyper-responsiveness supports that individuals with SCI have the capacity to activate the right FG and configurally process when necessary for the successful completion of a task. This significantly greater activation provides evidence for the functional integrity of the right FG in these young men with SCD and may also reflect increased attention to the facial expressions in the high functioning individuals with SCI. There was no evidence for a predisposition toward feature-based processing or compensatory use of this style of perceptual processing based in the ITG (18) in individuals with SCD during the non-inverted condition of the DFEP. Hence, the non-inverted condition of the DFEP provides evidence for configural processing in individuals with SCI, as proposed in the enhanced local perceptual precedence hypothesis (225) and the recently proposed revised account of weak CC theory (411), but no evidence of a local perceptual precedence supported in the ITG ROI in the high functioning individuals with SCD, who participated in this study.

The inverted condition of the DFEP was designed to require feature-based processing to determine if the proband and brother groups would demonstrate comparable expertise during the attribution of emotion from dynamic facial expressions and investigate for enhanced local perceptual precedence in the proband group. There were no significant differences in left FG or right and left ITG activations in either the non-inverted or the inverted condition of the DFEP between groups. Hence, these studies did not provide evidence of feature-based perceptual processing supported by these ROI to support enhanced local perceptual precedence in the proband group (18). However, from the literature it is not clear if these are the only relevant ROI in feature-based processing or if other regions, as discussed in a recent review of the enhanced local perceptual precedence hypothesis, are also involved (225). Interestingly, in both the proband and brother group ITG activation was indirectly correlated with response time in the inverted condition of the DFEP providing evidence that the greater the ITG activation the faster the attribution of emotion from inverted dynamic facial expressions in both groups.

This dimensional fMRI study has implications for the development of an integrated model for SCI. Although the SCI and expertise measures support a relationship between SCI and expertise in the attribution of emotion, accuracy- response time strategies need to be better understood to enable a better understanding of the relationship between the behavioural and cognitive levels of explanation for SCI. The indirect and direct correlation between SRS score and right FG activation during the attribution of emotion in the non-inverted and inverted conditions of the DFEP respectively, provide evidence of a relationship between the right FG and autistic symptomatology measured using the SRS. This supports a relationship between the behavioural and functional levels of explanation for SCI; however, individuals with SCI appear to adopt a task-dependant visual perceptual processing style and this needs further investigation. Further studies are required to determine the task-dependant factors that result in right FG hyper-responsiveness and right FG hypo-responsiveness in individuals with SCI before developing any tentative model of SCI.

Further studies should include WBA to determine the pattern of activation across all brain regions and identify functional ROI during the DFEP. These studies should use conjunction, factorial and parametric experimental designs and tighter control conditions to determine the specific activations associated with isolated CCI for each of the tasks. More powerful rapid presentation ER-fMRI studies should be undertaken that investigate ROI activation specifically related to accurate responses. This method would allow activation at the time the emotion is attributed from each dynamic facial expression to be isolate. More temporally specific HRF models are required to account for differences in the temporal relationship between the event and the activation in different brain areas. GSR and basal heart and breath rate should be measured to model autonomic arousal during the paradigm. Most importantly eye-tracking technology needs to be incorporated to determine the relationship between configural processing and attention and elucidate the relationship between autistic symptomatology, configural processing and right FG ROI activation in these high functioning individuals with SCD and their brothers.

Chapter 10 Synthesis of the Dimensional Studies

10.1 Discussion of the Dimensional Studies

Explanatory models that integrate evolution, development, behavioural, cognitive and functional levels of explanation for SCI have the potential to progress the aetiological study of SCI. In integrated aetiologically valid explanatory models, findings from all levels of explanation would constrain and inform each other (4, 5), to reduce the heterogeneous nature of the social phenotype studied in autism (11). Aetiologically valid explanatory models for SCI would ideally integrate evolutionary, developmental, behavioural, cognitive and functional levels of explanation for SCI. The dimensional studies were undertaken to inform the development of an integrated aetiologically valid explanatory model for the SCI seen in high functioning individuals with SCD.

SCI, measured as a dimension of behaviour, and right FG specialisation for the configural processing of faces are argued to both fulfil the evolutionary and developmental trajectory criteria for an aetiologically valid construct and integrate an aetiologically valid behavioural, cognitive and functional levels of explanation for the SCI. Therefore, these constructs were considered potentially informative in the development of an integrated explanatory model for the SCI. The dimensional studies presented in this thesis focused on the relationship between the behavioural, cognitive and functional levels of explanation to inform and constrain the further development of an explanatory model for SCI, as seen in ASD.

Categorical approaches to the classification of behaviour, such as ASD diagnosis, remain subjective and the lack of clear inclusion criteria for PDD-NOS has led to the exclusion of individuals with this subtype of ASD from research studies. Recent epidemiological studies have shown that PDD-NOS is at least twice as common as autism in the general community and that ASD other than autism show the greatest rate of increase in the general population (80, 83). Therefore, the exclusion of PDD-NOS represents the exclusion of the commonest sub-type of ASD considerably reducing the power of aetiological studies of SCI. Recent factor analysis found that all autism symptoms, related to social processes, factored onto one autistic symptom dimension fitting with the notion of autism as a unitary syndrome (358). Research supports the conceptualisation of autism as the upper extreme of a social communication continuum and advocates the study of SCI as a dimension of behaviour (3). The dimensional studies addressed the diagnostic uncertainty inherent in the categorical diagnosis of ASD by quantifying autistic social symptomatology as a dimension of behaviour. The quantification of continuously distributed characteristics is a more powerful approach for aetiological studies (326). Quantification of continuously distributed characteristics, and the creation of a continuum of affectedness, offered the opportunity to include those with SCI who did, and those that did not, fulfil criteria for a diagnosis of autism or AS and identify relatives expressing the BAP in the dimensional studies. Quantifying autistic social symptomatology also permitted the informative inclusion of the male siblings of young men with SCD in the fMRI dimensional study.

The SRS, which measures autistic social impairment as a dimension of behaviour, was used to quantify the social symptomatology in the dimensional studies. Previous studies, using the SRS, have not attempted to identify the underlying cognitive or functional aetiology of SCI. Potential limitations of

such a behavioural dimension, in terms of explanatory modelling include that SCI, as measured by the SRS, may result from the intersection of complex developmental processes and, potentially, also be heterogeneous (14) complicating the identification of underlying cognitive, functional and genetic actiologies. The SRS also may not measure an aetiologically relevant dimension of behaviour. While acknowledging these limitations, the dimensional studies in this thesis sought to identify the underlying cognitive and functional aetiology of SCI in individuals with SCD. The initial dimensional study compared the SRS scores of those who did, and those that did not, attract an ADI-R diagnosis of autism to allow comparison of the dimensional fMRI study with the categorical studies earlier in the thesis and other studies of autism. The overarching hypothesis of the dimensional studies was that quantification of SCI would facilitate integrated research to determine if reduced expertise in the attribution of emotion from developing facial expressions secondary to reduced right FG specialisation for the configural processing of facial expressions offers an explanation for the SCI seen in ASD.

Dimensionalisation of autistic social symptomatology was undertaken for 60 probands to determine: if diagnosis differentiated groups based on the severity of SCI; or, if SCI could be quantified across diagnostic boundaries to facilitate the study of cognitive and functional explanations of SCI in the dimensional fMRI study. In the dimensional fMRI study, dimensionalisation of autistic social symptomatology was undertaken for all FDR to determine the mean SCI and the range of SCI in the FDR of these high functioning young men with SCD. The dimensional fMRI study then focused on the relationship between the dimensional measurement of SCI, measurement of expertise in the attribution of emotion and quantification of the neural correlates of emotion attribution from dynamic facial expressions in high functioning men with SCD. Specifically, fMRI was used to measure activation in the right FG and ITG ROI to investigate if configural processing supported by the right FG, or predisposition toward the feature-based processing of non-inverted faces supported by the ITG, provided an explanation for SCI in young men with SCD during the attribution of emotion from non-inverted dynamic facial expressions. The activation in these ROI was also measured during the attribution of emotion from inverted dynamic facial expressions to determine if the high functioning young men with SCD would have comparable ROI activation when they attributed emotion from inverted facial expressions or if they would demonstrate enhanced local perceptual precedence as recently proposed in autism (222).

The behavioural findings of the dimensional studies confirmed that these high functioning young men with SCD have significantly greater autistic SCI than their FDR. Interestingly, the fathers of these high functioning young men with SCD had significantly greater SCI than the mother, female and male siblings. This finding supports the existence of BAP in the families of individuals with SCD and fits with the male preponderance of SCI, as reported in ASD, particularly in individuals of normal intelligence (80). High functioning young men with SCD with, and without, a diagnosis of autism had qualitatively and quantitatively similar SCI providing evidence that diagnosis did not differentiate diagnostically distinct groups based on the severity of SCI as previously proposed (3).

The fMRI findings of the dimensional studies provided evidence that the SCI impairment was directly related to accuracy across groups, but these were not in the hypothesised direction. There was a trend

towards a significantly greater response time during the attribution of emotion from non-inverted dynamic facial expressions in the SCD group suggesting the use of an accuracy-response time trade off in the proband group. There were correlations between right FG and SCI for the non-inverted and inverted condition of the DFEP, but these too were not in the hypothesised direction. The dimensional studies found that right FG activation was indirectly correlated with SCI in the non-inverted condition in the DFEP and directly correlated with SCI in the inverted condition of the DFEP; however, both groups had comparable accuracy in the non-inverted condition of the DFEP. The group differences in right FG activation were in keeping with the direction of the correlations, but contrary to the hypothesis that individuals with SCI would have reduced right FG specialisation for the configural processing of face percepts in the non-inverted condition of the DFEP. The proband group actually activated significantly greater right FG ROI than the brother group to achieve a comparable performance during the attribution of emotion from non-inverted dynamic facial expressions. However, to achieve a comparable performance during the attribution of emotion from inverted dynamic facial expressions the proband group required to activate significantly less right FG ROI than the brother group. Interestingly, although individuals with SCD had comparable performance and ITG ROI activation to their brothers in the non-inverted and inverted conditions of the DFEP, ITG activation was indirectly correlated with response time during the attribution of emotion from inverted dynamic facial expressions across both groups providing evidence that ITG activation supports faster attribution of emotion from inverted facial expressions.

10.2 Conclusions of the Dimensional Studies

Transgression of diagnostic boundaries in the initial dimensional study and quantification of autistic social symptomatology using the SRS in young men with SCD effected the informative inclusion of individuals with SCI in this fMRI study. Previous studies using the SRS, which measures autistic social symptomatology, support the quantification of autistic symptomatology as a dimension of behaviour (358). Quantification of autistic symptomatology effected the recruitment of high functioning young men with SCI as seen in autism, whether they had a diagnosis of autism. The use of the SRS to quantify autistic symptomatology also allowed the quantification of autism symptomatology and identification of the broader phenotype in the FDR of young men with SCD. Identification of the BAP, particularly the male sibling group, who have previously been reported to express BAP (376) informed the recruitment of brothers into the fMRI study. All of the probands and none of the brothers recruited for this fMRI study were above the threshold for autism on the social impairment sub-domain of the ADI-R and all had a SRS score in the range previously reported for PDD-NOS (13). Contrary to the hypothesis, the findings of the dimensional studies did not support the conceptualisation of autism as the upper extreme of the social communication continuum in this groups of high functioning young men with SCD (3). The findings did support the quantification of SCI across diagnostic boundaries and inclusion for individuals with and without a diagnosis of autism in the initial dimensional studies facilitating an 'integrative' research approach to the development of an explanatory model for SCI.

The 'integration' of different levels of investigation in the dimensional fMRI study identified that SCI was directly related to accuracy, but not response time, in the attribution of emotion from inverted facial

expressions. At first this did not appear to be in keeping with the hypothesis that individuals with SCI would have reduced expertise in the attribution of emotion. However, the significantly different response time in the proband group suggests that they may indeed have reduced expertise in the attribution of emotion from non-inverted dynamic facial expressions. Possible explanations for the lack of relationship between accuracy and response time during the attribution of emotion include: non-linear relationship between these variables and accuracy-response time trade-off strategy while processing facial expressions.

SCI and right FG hypo- and hyper-responsiveness were found to be both correlated and associated constructs during the attribution of emotion from facial expressions. However, neither of these constructs were correlated or associated in the hypothesised directions in the dimensional fMRI study. There was a direct relationship between SCI and right FG activation in the non-inverted condition of the DFEP, which requires configural processing and, an indirect relationship between SCI and right FG activation in the inverted condition of the DFEP, which did not require configural processing. High functioning young men with the greatest SCI activated the greatest right FG activation to achieve comparable accuracy during the attribution of emotion from non-inverted dynamic facial expressions and the lowest right FG activation to achieve comparable accuracy during the attribution of emotion from inverted dynamic facial expressions. This was contrary to the hypothesis that SCI would be related to reduced right FG activation and provides evidence for the use of a compensatory strategy, which involves greater right FG activation to configurally process the non-inverted facial expressions, in those with the greatest SCI.

Although, the high functioning young men with SCD and their brothers had comparable accuracy during the attribution of emotion in both the non-inverted and inverted condition of the DFEP, which allows comparison of brain activation between groups (39), this comparable accuracy was found to be associated with significantly different right FG activations in the non-inverted and inverted condition of the DFEP. Previous studies have reported right FG hypo-activation during the attribution of emotion from static facial expressions in individuals with ASD (314). The literature also supports feature-base processing supported in the ITG in autistic individuals (18) and local perceptual precedence in ASD (225). Therefore, it was hypothesised that the proband group would have reduced expertise associated with right FG hypo-responsiveness and potentially demonstrate enhanced local perceptual precedence though the use of feature-based strategies supported in ITG ROI in the non-inverted condition of the DFEP. However, probands demonstrated right FG hyper-responsiveness, and did not demonstrate enhanced local perceptual processing in the ITG, during the non-inverted condition of the DFEP. Therefore, this hypothesis was not supported and did not offer an explanation for the SCI in individuals with SCD.

Models for the right FG specialisation for the configural processing of faces model assume either that inverted faces are not as important to human beings or that humans do not gain experience with inverted facial expressions and, hence, do not develop right FG specialisation for the configural processing of inverted dynamic facial expressions (242). In the inverted condition of the DFEP, it was hypothesised

that both groups would use comparable feature-based strategies for the perceptual processing of inverted facial expressions and that this would be associated with comparable neural activation in both groups. However, the SCD group used significantly less right FG activation than the brother group in the inverted condition of the DFEP. The right FG hypo-responsiveness findings in the inverted facial expressions condition of the DFEP in the individuals with SCD provides evidence of a predisposition toward configural processing in individuals who do not have SCI, even when facial expressions are inverted. Previous studies have reported holistic processing (403) and right FG activation during the processing of inverted faces in typically developing individuals (412). Possible explanations for the right FG hyper- and hypo-responsiveness seen in the non-inverted and inverted condition of the DFEP include condition-dependant right FG activation in response to configural processing and/ or attentional demands of the different conditions presented in the DFEP and will be discussed more fully in the next chapter. This condition-dependant right FG hypo and hyper-responsiveness in individuals with SCD suggests the versatility and abilities of face processing in persons with autism as previously reported may have been underestimated (413). However, these findings did not support the hypothesis that SCI was related to reduced expertise in the attribution of emotion as a consequence of reduced specialisation of the right FG for configural processing of dynamic facial expressions. Therefore, this hypothesis did not offer an explanation for the SCI in individuals with SCD.

In terms of an integrated explanatory model for SCI, the hypotheses in the dimensional study that: (i.) individuals with SCD would be less expert than their brothers in the attribution of emotion from non-inverted (upright) dynamic facial expressions related to reduced right FG ROI specialisation for the configural processing of dynamic facial expressions; and (ii.) they would, potentially, use enhanced local perceptual precedence were not upheld. Although, there was a relationship between SCI and right FG activation in both the non-inverted and inverted conditions of the DFEP neither relationship was in the hypothesised direction. The hypothesis that SCI was related to reduced accuracy or increased response time during the attribution of emotion from dynamic facial expressions was not upheld. In the non-inverted task, SCI was related to increased accuracy suggesting accuracy-speed trade-offs. In the inverted task, there was a trend toward an indirect relationship between response time and SCI suggesting the use of a faster alternative perceptual strategy in those with the greatest SCI. Reduced brain activation in the right FG during the attribution of emotion from dynamic facial expressions was condition-dependant in high functioning young men with SCD. In the non-inverted condition of the DFEP, which required configural processing to attribute emotion from non-inverted dynamic facial expressions, the high functioning young men with SCD had greater right FG activation than their brothers. This was contrary to the hypothesis and provided evidence for right FG specialisation for the configural processing of facial expressions in these high functioning young men with SCD. However, the high functioning individuals with SCD activated the right FG significantly more to achieve comparable performance to their brothers in the non-inverted condition of the DFEP, and significantly less to achieve comparable performance to their brothers in the inverted condition of the DFEP. Hence, providing evidence that right FG activation is condition-dependant and related to configural processing/ attention allocation in individuals with SCD. Individuals with autism have been argued to have a predisposition toward enhanced local perceptual processing for individual face parts, despite intact

configural processing of individual face parts (414). There was no evidence of a predisposition toward the feature-based processing of non-inverted faces supported by the ITG in high functioning young men with SCD and their brothers. Individuals with SCD had comparable performance associated with comparable activation in the ITG ROI in the inverted condition of the DFEP. However, other regions of the brain may support enhanced local perceptual precedence in individuals with SCD and qualitative fMRI studies should be undertaken to investigate for activation out with the FG and ITG ROI. Reduced right FG was related to the inverted dynamic facial expression processing paradigm, which could be undertaken without the configural processing of face percepts. This was contrary to the hypothesis that individuals with SCD would be as expert than their brothers during the attribution of emotion from inverted facial expressions related to comparable neural activation during the attribution of emotion inverted dynamic facial expressions.

Dimensionalisation of autistic symptomatology did facilitate behavioural, cognitive and functional levels of investigation, and further investigation for an explanation for SCI in high functioning young men with SCD. The dimensional studies to date have investigated the potential explanatory validity of emotion attribution from dynamic facial expressions at the behavioural, cognitive and functional levels of explanation for the SCI, and found evidence for a relationship between SCI, measured as a behavioural dimension, and activation in the right FG during the attribution of emotion from dynamic facial expressions. The dimensional fMRI study implicated the right FG ROI, but not the ITG ROI, in an explanatory model for SCI seen in autism. The fMRI study found that right FG, but not ITG, activation during the attribution of emotion from dynamic facial expressions distinguished high function young men with SCD from their brothers and was associated with SCI. The dimensional fMRI study provided further evidence of atypical perceptual processing in individuals with SCD, who all had SCI in the range seen in ASD. This potentially allows the development of a preliminary explanatory model for SCI in which right FG activation directly predicts SCI during the processing of non-inverted facial expressions and right FG activation indirectly predicts SCI during the processing of inverted facial expressions. However, the factors that determine the condition-dependant mechanism(s) remain elusive and require further study in future fMRI experiments before any explanatory model for SCI is tentatively proposed.

10.3 Implications of the Dimensional Studies

The dimensional studies have the following implications for the development of an integrated model for SCI. They highlighted the utility of SCI, measured as a dimension of behaviour, in determining the relationships between SCI and cognitive and functional levels of explanation and the complexity of the relationships between these different levels of explanation. The relationship between the behavioural and cognitive levels of explanation for SCI highlights the possible contribution of strategies such as accuracy-response time to the relationship between behaviour, cognition and brain activation, and the need for fMRI to elucidate these complex relationships. The indirect and direct correlation between SRS score and right FG activation during the attribution of emotion in the non-inverted and inverted conditions of the DFEP respectively, highlights that the relationship between the behavioural and functional levels of explanation for SCI can be condition-dependant in fMRI experimentation and that cognitive mechanisms such as visual perceptual processing style are sensitive to condition-dependant

factors. These findings highlight the need for further investigation to determine the inherent strategy and condition-dependant factors that result in accuracy-speed trade-offs and right FG hyper- and hypo-responsiveness in these high functioning individuals with SCD before the further development of an integrated model for the SCI. The following chapter explores the apparently paradoxical findings of the dimensional study in terms of the categorical studies in this thesis and other literature on face and facial expression processing in ASD.

PART IV: CONCLUSION

Chapter 11 Emotion Attribution from Facial Expressions in High Functioning Individuals with Social Communication Impairment

11.1 Discussion of the Categorical and Dimensional Studies

The categorical and dimensional studies presented in this thesis were preliminary studies undertaken to develop an integrated explanatory model for SCI as seen in ASD. Integrated approaches, which are constrained at the evolutionary, developmental, behavioural, cognitive and functional levels of explanation, are required to inform the development of an explanatory model for the SCI in ASD (4, 5). Biologically valid explanations for SCI arguably would have an evolution, a developmental trajectory, and 'integrate' behavioural, cognitive and functional levels of explanation for SCI into an explanatory model for the SCI seen in ASD. Previously presented research on social communication and the configural processing of face and facial expressions support both as biologically valid constructs at the evolutionary and developmental levels of explanation for SCI. Reduced expertise in the attribution of emotion from facial expressions is recognised as an under-researched, yet credible explanation for the SCI seen in individuals with autism (1) and, potentially, reduced right FG specialisation for the configural processing of facial expressions offers an explanation for this phenomena. Therefore, the categorical and dimensional studies focused on these constructs and investigated the theoretical conception that SCI in ASD is related to reduced right FG specialisation for the configural processing of face percepts and, consequent, reduced expertise in the attribution of emotion from facial expressions. Specifically, both the categorical and dimensional studies investigated this hypothesis at the behavioural, cognitive and functional levels of explanation as a possible model for the SCI seen in ASD.

The categorical fMRI studies presented in this thesis extended previous work in this area by investigating emotion attribution from static facial expressions in high functioning individuals with diagnosis of both HFA and AS. In the initial categorical fMRI study, neural activation in the right FG, amygdala and prefrontal ROI, known to be activated during the attribution of emotion from facial expressions in typically developing individuals, was measured. High functioning individuals with ASD were found to have comparable prefrontal ROI activation during the attribution of emotion from static facial expressions in the EL and EM tasks presented in the EAP. Individuals with ASD have been reported to have reduced activation in the prefrontal cortex associated with TOM deficit (169, 279). However, in a recent study high functioning individuals with ASD, who were less accurate than controls, did not have significantly different prefrontal activations when asked to explicitly attribute emotion from static facial expressions (8). Hence, prefrontal activations in individuals with ASD have previously been reported as comparable to typically developing controls during the attribution of emotion from static facial expressions in explicit attribution tasks such as the EL task. Therefore, prefrontal findings in the EL task presented in the EAP in the initial categorical study were congruent with other studies of emotion attribution from static facial expressions and did not provide an explanation for the SCI seen in ASD.

The high functioning individuals with ASD in the initial categorical study were also found to have comparable amygdala ROI activation during the attribution of emotion from static facial expressions in the EM task, an implicit emotion attribution task. Previous studies have suggested that individuals with ASD have a reduced innate predisposition to engage in social interactions (318) and are less attentive to faces (157, 326). Those implicating amygdala dysfunction in autism have proposed that reduced activation of this region is associated with reduced emotional salience of facial expressions and consequent SCI observed in individuals with ASD (272-274). FMRI studies have found reduced amygdala activation in tasks that require individuals with ASD to attribute the gender from neutral faces (6). Reduced amygdala activation has also been reported in high functioning individuals with ASD in tasks that required the attribution of complex emotions from stimuli that show only the eyes region of the face (274). However, other studies have found that high functioning individuals with ASD, who were less accurate in the explicit attribution of emotion from static facial expressions, have relatively preserved amygdala activation (8) and that individuals with ASD who fixated on the eyes region of the face actually had increased amygdala activation (203). The comparable amygdala activation in the EM task of the EAP in the initial categorical fMRI study provided evidence that facial expressions are of comparable social salience to these high functioning individuals with ASD. This finding also suggests that these individuals with ASD have accrued some experience with face percepts and will have relative experience-dependant specialisation of the right FG for face processing. The comparable amygdala findings across groups in the initial categorical fMRI study, therefore, did not provide an explanation for the SCI seen in these individuals with ASD.

Ultimately, investigation of the prefrontal and amygdala ROI did not provide any explanation for the SCI in these high functioning individuals with ASD in the categorical fMRI studies. However, in contrast to the typical prefrontal and amygdala activation, individuals with ASD did demonstrate reduced right FG activation associated with the attribution of emotion from static facial expressions in the EM task, but not the EL task, of the EAP. On consideration of the experimental tasks, it became apparent that the reduced right FG may actually be related to the inherent task-dependant differences such as: differences in language facilitation; implicit and explicit instruction and processing demands; differing inherent perceptual/ configural load; and, ability to adopt differing perceptual processing styles for the successful completion of the respective tasks. Also confounding factors such as: reduced attention to the eyes region of the face or whole face could also be contributing to the reduced right FG activation demonstrated in the EM task of the EAP in the initial categorical fMRI study.

To clarify these factors and determine if right FG activation atypicalities were related specifically to facial expression as opposed to face processing in ASD a second categorical fMRI study was undertaken. This study used an implicit face processing task called the GAP, which did not incorporate language facilitation and required attention to the eyes region of the face, to clarify if right FG activation atypicalities were related specifically to facial expression as opposed to face processing in ASD. This second categorical fMRI study found that, despite attention to the eyes region of the face, this implicit face processing task was also associated with reduced right FG activation providing evidence for atypical perceptual processing in face and facial expression processing paradigms in ASD.

The categorical fMRI studies provided evidence that young men with ASD demonstrate comparable right FG activation when attributing emotion in explicit emotion attribution tasks that require configural processing for their successful completion; and, reduced right FG activation when attributing emotion from implicit emotion attribution tasks do not require configural processing for their successful completion. Individuals with ASD had the capacity to configurally process face percepts when necessary for the completion of the task, but used atypical face processing strategies in implicit tasks with, potentially, greater perceptual load that did not necessitate configural processing. These categorical studies supported that task-dependant atypical perceptual processing in ASD was not related to reduced attention to the eyes region of the face *per se*. However, they did not rule out that the perceptual atypicalities may relate to a reduced capacity to configurally process face percepts and/ or reduced attention to the whole face percept in ASD. Hence, the categorical fMRI studies provided evidence for visual perceptual, but not cognitive or emotional, atypicalities during the attribution of emotion from static facial expressions in high functioning individuals with ASD.

The dimensional studies extended the research on emotion attribution undertaken in the categorical fMRI studies by quantifying autistic social symptomatology in high functioning young men with SCD and their FDR. The dimensional studies focused on high functioning young men with SCD, who had qualitatively and quantitatively similar SCI to that seen in autism, irrespective of whether they had an ADI-R autism diagnosis. The initial dimensional study found that quantification of SCI did not differentiated distinct diagnostic groups in 60 young men with SCD, supporting the quantification of SCI across diagnostic boundaries to facilitate integrative research. From this larger group, 10 young men with SCD with brothers within 4 years of age were recruited for the dimensional fMRI study. This dimensional fMRI study investigated for correlations, as well as associations, between SCI measured as a dimension of behaviour and neural activation during the attribution of emotion from non-inverted and inverted dynamic facial expressions in these young men with SCD and their brothers. Emotion attribution from dynamic facial expressions was studied using a paradigm that required configural processing and continuous attention to the whole face during the development of each facial expression. This paradigm called the DFEP was designed to be a more naturalistic dynamic facial expression processing paradigm, with more comparable face processing demands to facial expression processing in actual social situations. The paradigm was designed to address some of the limitations inherent in the EAP and GAP used in the categorical fMRI studies. Namely, the paradigm involved: explicit attribution of emotion; did not contain language facilitation; required attention to the whole face; and, continuous configural processing of each developing facial expression. Neural activation in the FG and the ITG ROI, known to be involved in the perceptual processing of non-inverted and inverted facial expressions in typically developing individuals, was investigated for associations with diagnosis and correlations with expertise in the attribution of emotional from non-inverted and inverted dynamic facial expressions and SCI.

The dimensional fMRI study found that the SCI was directly related to accuracy across the proband and brother groups in the non-inverted condition of the DFEP. The proband group was as accurate as the brother group in the non-inverted condition of the DFEP. However, there was a trend toward increased response time in the proband group when compared to the brother group. This increased response time

suggests that the probands may have relatively reduced expertise in the attribution of emotion from non-inverted facial expressions or may have used an accuracy-weighted strategy in the non-inverted condition of the DFEP. SCI was directly correlated with right FG activation across the groups and the proband group activated significantly greater right FG activation to achieve a comparable level of performance as the brother group in the non-inverted condition of the DFEP. Although, contrary to the hypothesis, individuals with SCD did not have statistically significant reduction in expertise in the attribution of emotion from non-inverted dynamic facial expressions using either accuracy or response time as proxy measures for expertise. Indeed, the trend toward increased response time in the proband group supports the need for further investigation in better powered studies. However, the hypothesis that SCI would be secondary to reduced right FG specialisation for the perceptual processing of faces, when task necessitated configural processing of an upright developing facial expression, was definitively unsupported. Paradoxically, the ASD group demonstrated statistically greater right FG activation than their brothers to achieve comparable performance attributing emotion from non-inverted facial expressions.

There was no significant difference in accuracy or response time between the proband and brother group in the inverted condition of the DFEP supporting that both groups have comparable expertise in the perceptual processing of inverted facials expressions. There was a trend toward a direct correlation between SCI and response time and SCI was indirectly correlated with right FG activation across groups. The proband group activated significantly less right FG to achieve a comparable level of performance to the brother group in the inverted condition of the DFEP. The brother group demonstrated greater right FG activation during the perceptual processing of inverted facial expressions suggesting that the individuals without SCI use configural processing during the attribution of emotion from inverted facial expressions. There was no evidence to support a predisposition toward or compensatory mechanism involving the use of feature-based processing supported in the ITG or left FG ROI in the inverted condition of the DFEP in any either group. However, across groups ITG activation was directly related to response time during the attribution of emotion from inverted facial expressions.

The dimensional studies support that individuals with SCI have the capacity to accurately attribute emotion from non-inverted dynamic facial expressions. Individuals with the greatest SCI were the most accurate; however, the proband group had to activate the right FG significantly more than the brother group to achieve a comparable performance during non-inverted condition of the DFEP. Increased right FG during the attribution of emotion in the non-inverted condition of the DFEP may be related to the increased configural processing demands inherent in the condition or to the increased attention required to attribute emotion from dynamic facial expressions. Alternatively, increased accuracy may be as a result of an accuracy/ response time trade-off strategy in the non-inverted task. This might be related to the attribution of emotion later in the development of the dynamic facial expression, as eluded to by the trend toward a significantly slower response time. However, response time and right FG activation were not found to be linearly related in the non-inverted condition of the DFEP. The trend toward a direct relationship between SCI and response time in the inverted task provides evidence that in a larger sample those with the greatest autistic symptoms would, potentially, be the fastest in attributing emotion from

inverted dynamic facial expressions. Possible explanations for the proband group activating significantly less right FG activation than their brothers when attributing emotion from inverted dynamic facial expressions include: decreased innate predisposition to attend to inverted faces and/ or a decrease innate predisposition to configurally process inverted faces in the SCD group; and, a greater innate predisposition to attend to inverted faces or configurally process inverted faces in the brother group.

Paradoxically, the dimensional studies were undertaken to further explore reduced right FG specialisation for the perceptual processing of facial expression as an explanation for the SCI having identified an association between ASD, in which SCI is the core impairment, and task-dependent atypical right FG activation and perceptual processing during the attribution of emotion from facial expressions in the categorical studies. However, the investigation of SCI, expertise in the attribution of emotion and neural activation in the right FG in individuals with SCI in the categorical and dimensional studies resulted in some surprising insights into the nature of the relationship between these processes in the high functioning individuals with SCI studied. Accuracy and response time, which were measured as an indication of expertise in the attribution of emotion from facial expressions, provided evidence that individuals with SCI were not necessarily less expert than typically developing individuals in the attribution of emotion from static or dynamic facial expressions. Indeed, individuals with SCI had comparable accuracy to typically developing individuals across all paradigms. However, individuals with SCI had greater response times in those tasks that could be completed without configurally processing. Specifically, individuals with SCI had: comparable response time in the EL task and inverted condition of the DFEP; statistically greater response time in the EM task; and, demonstrated a trend toward an increased response time in the non-inverted condition of the DFEP. SCI was also unexpectedly related to right FG hyper- and hypo-responsiveness during the attribution of emotion from non-inverted and inverted facial expressions respectively. The following sub-sections examine these apparent paradoxes and propose further studies to determine the relationship between SCI, expertise in the attribution of emotion from facial expressions and right FG responsiveness in high functioning individuals with SCI.

11.1.1 Social Communication Impairment and Emotion Attribution

Given the emphasis in the diagnostic criteria on the combination of facial expression processing deficits and SCI in individuals with ASD, it is surprising that the nature of the relationship between these processes in normal development and in individuals with ASD in particular has not received further attention (415). Having hypothesised that individuals with SCI would be less expert in the attribution of emotion from static and dynamic facial expressions, the categorical and dimensional studies provided evidence that the high functioning individuals with ASD were able to attribute emotion as accurately as typically developing individuals in the fMRI studies. Indeed, the dimensional studies found evidence of a statistically significant relationship between SCI and expertise in the attribution of emotion from dynamic facial expressions with accuracy, but not response time, directly correlated with SRS score. Importantly, there was also evidence of a trend towards significantly increased response time in the proband group compared to the typically developing brother group. Other studies have suggested that

given sufficient time individuals with SCI are able to attribute emotion from facial expressions (416) and the trend toward a significantly different response time seen in the dimensional study may be due to the use of an accuracy-weighted strategy in the proband group. The lack of correlation between response time and accuracy may relate to the use of an accuracy weighted strategy in some, but not all, of the individuals that participated in the dimensional fMRI study. The increased response time may also be due to slower motor response in the individuals with SCI, who are widely reported to have motor co-ordination issues (417). Individuals with SCI may also spend more time inspecting details and, therefore, demonstrate reduced speed in configural tasks. When designing further studies it should be borne in mind that slowed performance may arise in the motor systems as opposed to the perceptual system *per se* in individuals with ASD.

Replication of the findings of the dimensional fMRI studies with a larger sample would increase the power to determine which of the trends are statistically significant. Factor analytic studies in larger samples of individuals with SCI are also required to determine the degree to which expertise in the attribution of emotion from facial expressions explains the variance in SCI measured as a dimension of behaviour. Other potential explanations for the lack of relationship between SCI, measured using the SRS, and response time in the non-inverted DFEP may relate to the existence of a different factor structure for SCI in the high functioning young men, who participated in the dimensional studies compared to the population on which the SRS was previously administered (358). Factor analytic studies are needed to determine if SCI, as measured by the SRS, actually factors onto a single factor in these high functioning individuals with SCI. Another possible explanation for the lack of relationship between SCI and response time is that individuals with SCD exercise an atypical neural activation pattern to support the processing of dynamic facial expressions. In this scenario, one might also anticipate that there would not be any relationship between response time for the attribution of emotion from dynamic facial expressions and SCI in individuals with SCD. This atypical neural activation may represent a preferential strategy or a predisposition toward an atypical cognitive style in individuals with SCI when task completion does not necessarily require configural processing. Given the evidence for task-dependant configural processing in the individuals with SCI in both the categorical and dimensional studies, a predisposition towards an atypical perceptual processing style would account for the task-/ condition-dependant response time differences seen in the categorical and dimensional studies. The extent to which processing is locally biased and the extent to which configural processing is possible in individuals with ASD is an area of ongoing controversy in the autism literature (222). Previous literature has proposed that configural processing manifests as a function of the autistic individuals predisposition to adopt this style of perceptual processing (418). A predisposition toward an atypical processing style would explain the conflicting findings across tasks in the categorical and dimensional studies, which used paradigms with very different configural processing requirements. Further studies are required to determine if the adoption of an atypical perceptual processing approach represents a predisposition toward a detail-orientated style or represents a compensatory strategy to address a relatively reduced capacity for the configural processing of faces during the attribution of emotion from facial expressions. Further studies that tax configural processing mechanisms for successful task completion are necessary to

determine if the atypical perceptual processing seen in ASD represents a predisposition toward a detail-orientated style or a compensatory strategy to address a relatively reduced capacity for the configural processing of face percepts.

Despite the crucial contribution of facial expression to social communication and the social implications of not understanding facial expression, it has been unclear whether individuals with autism are impaired at recognizing facial expressions, or impaired in some more basic aspect of face processing like configural processing. Many studies have revealed difficulties with basic expressions (185, 213, 252), but many others have not (165, 253, 272, 290, 419). Other studies have suggested that individuals have an impairment with more subtle or cognitive expressions such as arrogance or flirtatiousness when viewing the eyes region of the face (165). If a specific facial expression processing deficit exists in autism, it is not evident whether all expressions are implicated and if so, whether this is to an equal extent. One study reported relative impairments in the recognition of anger and disgust (420), while another found that a group of children with autism were impaired at recognizing surprise, but not happiness or sadness (421). Many studies have supported a relative impairment in the recognition of fear, including a recent study using a large number of graded stimuli, which demonstrated clear deficits in the recognition of basic expressions, particularly affecting the recognition of fear, anger and disgust (422). The categorical studies support that individuals with ASD are not predisposed to configurally process face or facial expressions tasks unless an explicit requirement necessary for the successful completion of the task. This suggests that the predisposition toward/ capacity for configural processing, a basic aspect of face processing, is central to the face/ facial expressions processing deficits in ASD.

When considering the findings from fMRI studies it is important to recognise the effects of task-related differences in study design. For example, the recent study using graded stimuli mentioned, used an implicit face processing task in which individuals with ASD were asked to determine the 'sex' of the person presented in the face picture rather than to attribute emotion from the facial expression. The use of an implicit processing task and failure to ensure attention to the eye regions of the face when the more threatening facial expressions were displayed may have contributed to the right FG hypo-responsiveness reported in the ASD group in this study. Other researchers have proposed different hypotheses to account for the variability seen in the results from basic facial expression studies. Some have suggested that the reason for the lack of consensus relates to the fact that the impairments in processing basic facial expressions are relatively subtle in high functioning individuals with autism (165). Others have argued that facial expression recognition deficits exist even in high functioning individuals with autism, but that more subtle, fine-grained methods are necessary to detect them (422). While others have proposed atypical perceptual processing related to task-dependant differences in high functioning individuals as an alternative explanation for the variability in findings from these facial expression processing studies (413), which would also offer a possible explanation for the occurrence of processing deficits during face identity and recognition paradigms in ASD.

Intuitively, reduced expertise in the attribution of emotion from facial expressions is more lightly to be associated with the SCI than facial identity/ recognition deficits in individuals with ASD. However,

most studies have focused on facial identity/ recognition in ASD. A recent study of facial expressions and facial identity in individuals with SCI found that individuals with impaired and non-impaired facial identity processing were just as proficient at processing facial expression, and surmised that the processing of facial identity and the processing of facial expressions are dissociable consistent with current cognitive models of face processing. The authors of this study argued that this dissociation goes against the hypotheses that the social dysfunction causes a generalized failure to acquire face processing skills and argued that there must be another cause for the SCI seen in ASD (423). However, as this study did not compare face processing that was unrelated to facial identity recognition with the processing of facial expression for a generalized perceptual face processing deficit, this study did not excluded a deficit in face processing in ASD as an explanation for both these contingencies.

Previous studies have advocated that the development of SCI in some individuals may occur secondarily to different types of face processing impairments, whilst in other individuals the social dysfunction may occur secondarily to other primary deficits not associate with face processing (11). Indeed, studies of individuals with congenital prosopagnosia have found that these individuals, who have marked impairments on global/ local tasks similar to individuals with autism, do not exhibit the social deficits seen in autistic individuals (424). This raises the possibility that the social deficit and the perceptual disorder may be secondary to a common primary deficit and work in parallel. This would suggest that the later attribution of emotion in the EM task and the non-inverted condition of the DFEP may be related to some other construct that was not measured in either the categorical or the dimensional studies. Hence, the primary deficit combined with the lack of experience and the inadequate attention to faces may limit the acquisition of the normal configural perceptual skill (11). A contribution to the SCI from such parallel processes would be in keeping with the lack of relationship between SCI and expertise in the attribution found in the categorical and dimensional studies. However, developmental studies would be necessary to determine which processes are primary, which are inter-related, and which are developmentally distinct in individuals with SCI.

Others studies have proposed that face processing is slowed not solely because faces are social, but because they represent a particularly complex visual stimulus that depends specifically on configural processing. This view is supported by a recent study that showed that face recognition was not correlated with ratings of social impairment or associated with a particular ASD diagnosis. Instead, the authors propose that any difficulties in face processing in individuals with social deficits may be causally related to an underlying perceptual alteration (11). Previous studies have argued for an altered perceptual profile in autism based on differences in reaction time between neurotypical and autistic subjects in configural processing tasks (424). This would be in keeping with the differences in response time seen between tasks in the EAP in the categorical studies and trend toward increased response time seen in the non-inverted condition of the DFEP in the dimensional studies. Whether the perceptual alteration is primarily responsible for the local bias and/or difficulty to derive configuration or whether the atypical perceptual processing comes from a lack of experience with faces remains to be determined. Future studies require to determine if face processing atypicalities occur as a primary factor or are secondary to the social dysfunction and lack of experience with faces, or if some other common factor exists for both the SCI

and the face processing atypicalities in individuals with SCI. Even if the perceptual alteration was the cause of the social disability, perceptual performance and SCI are not mutually exclusive and each may contribute both to the difficulties in processing faces and to the difficulties in configural processing in individuals with SCI. The challenge is to understand in greater detail the relative and joint contributions of SCI and atypical perceptual processing during the attribution of emotion from facial expressions in individuals with SCI. One possible future direction is to screen for face processing deficits in populations with SCI and epidemiologically ascertained populations. This approach will be extremely important to determine the degree of face processing heterogeneity and the extent to which SCI is related to face processing/ facial expressions processing deficits in ASD. Indeed, recent studies of facial identity recognition have highlighted that not all individuals with ASD have facial identity processing issues, and support different patterns of facial identity processing impairments in individuals with SCD, providing evidence of face identity processing heterogeneity in individuals with ASD (11). The heterogeneity of facial expressions processing, however, still requires to be studied in individuals with ASD. The confusing relationship between SCI and expertise in the attribution of emotion in the dimensional studies may also be due to facial expression processing heterogeneity in the samples recruited. Future studies are need to determine if ASD is a heterogeneous syndrome characterized by different patterns of facial expression processing impairments or if there are multiple explanations for the SCI seen in ASD.

11.1.2 Emotion Attribution and Fusiform Gyrus Responsiveness

Although, the FG is generally considered a key area for processing faces (244), opinion is divided on the mechanism of development of expertise in face processing. Kanwisher and colleagues have proposed that right FG specialisation for expert face processing has an innate developmental trajectory, whereas Gauthier and colleagues have proposed that expert face processing requires experience-dependent specialisation of the right FG. The development of expertise for face processing in both models has been related to the configural processing of face percepts. Developmentally, this is associated with the progression from feature-based perceptual processing to configural perceptual processing supported in the FG (425) in typically developing individuals. Most studies of perceptual expertise have focused on facial recognition or the recognition of other exemplars for which the individuals has developed an expertise such as birds. Indeed, expertise has been defined as the capacity to individualise exemplars such as individual faces or birds and improved expertise in the individualisation of exemplars associated with increased accuracy and reduced response time (209). As faces are one of the most individualised exemplars, it is the exemplar for which the most people have developed the greatest expertise. Despite this impressive literature on expertise in facial recognition processing, there is a paucity of literature on the development of expertise for facial expression processing in typically developing individuals and individuals with ASD. Commonalities have been proposed such as the use of configural processing to process facial expressions, but the generalisability of these models of expertise development for facial recognition to the development of expertise in the attribution of emotion from facial expressions in typical development remains unclear. Some studies suggest facial identity and facial expression processing are dissociable (423) and others suggest that these constructs are not dissociable (259) in ASD. This is of crucial importance, as many face recognition studies have found reduced right FG activation related to face recognition deficits, a connection which is further substantiated by the literature

on acquired prosopagnosia. However, individuals with prosopagnosia do not demonstrate SCI as seen in ASD, therefore, either the right FG has to be associated with expertise in facial expressions processing or developmental studies of prosopagnosia need to show that individuals with developmental prosopagnosia have SCI to corroborate right FG involvement the expert attribution of emotion from facial expressions.

11.1.3 Social Communication Impairment and Fusiform Gyrus Responsiveness

The right FG responsiveness findings of the categorical and dimensional fMRI studies presented another apparent paradox. The dimensional fMRI study was undertaken to further interrogate the finding of right FG hypo-responsiveness during the attribution of emotion from static facial expressions identified in the categorical fMRI studies. However, the dimensional fMRI studies found right FG hyper-responsiveness during the non-inverted condition and right FG hypo-responsiveness during the inverted condition of the DFEP in the dimensional studies. Therefore, at first glance the findings of the dimensional fMRI study appeared counter-intuitive in relation to the findings of the categorical fMRI studies and the early literature on face processing in ASD. Indeed, the early literature on face and facial expression processing in individuals with ASD reported reduced (6, 18) and absent (6) right FG activation when viewing static face stimuli and reduced right FG when attributing emotion from static facial expressions (8). However, there is a more recent literature accruing in support of right FG activation during face processing in ASD (6, 203), which suggests that neural activation abnormalities are actually related to attentional deficits in ASD (203, 319). Previous studies proposed that the lack of attention to the eyes in autistic individuals may explain the lower right FG activation in the individuals with ASD (249). Indeed, when individuals with ASD fixate on a cross place between the eyes they demonstrate comparable right FG activation to typically developing individuals. Furthermore eye-tracking studies have shown that the greater the attention to the eyes the greater the right FG activation in the ASD group (203). However, as the ASD group did not show comparable attention to the eyes they demonstrated relatively lower right FG activation than the typically developing group in this particular study. This finding may also be due to relatively reduced expertise in configural processing of faces or because the tasks could be completed without configural processing or did not involve attributing emotion from facial expressions. However, it appears that the focus of the literature at present has shifted from configural processing of the face to attention to the eyes region of the face as a potential explanation for right FG findings in ASD. Reduced attention to the eyes has become conceptually appealing as an explanation for the reduced right FG activation. The eyes, particularly the sclera, have been shown to activate threat detection mechanisms mediated by the amygdala even when sclera from masked fearful/ angry facial expressions are viewed (426). Although it is well established that the amygdala is activated by threatening stimuli, as well as a variety of facial expressions, particularly fear (427), the amygdala also responds to happy and neutral facial expressions (269). It has been suggested that gaze aversion occurs in individuals with ASD to reduce the amygdala mediated autonomic hyper-arousal experienced when these individuals with ASD attend to the eyes region of the face (203). Further studies of autonomic arousal are needed to determine if high functioning individuals with SCI experience autonomic hyper-arousal when they attend to the eyes region of the face. Measurement of autonomic arousal was attempted during the categorical and dimensional fMRI studies, but was unsuccessful because of movement during the scan and soft ware malfunction during data acquisition, which affected collection of HR, respiratory rate and galvanic skin

response (GSR) conductance data. When debriefed after the DFEP, individuals with SCD did not relay that they had experienced anxiety to the facial expressions during the scan. However, future fMRI studies should compare these psycho-physiological measures to determine if this type of autonomic arousal occurs while individuals with ASD view the eyes region of the face as opposed to the whole face in the scanner.

Although reduced attention to the eyes region of the face is appealing as an explanation, the findings from the categorical studies provide evidence against this hypothesis; however, it still remains unclear if it is attention to whole face or configural processing of the face that is associated with right FG activation in these individuals with SCI. The lack of clarity is partially explained by the fact that the definition of configural processing is highly controversial and still the focus of ongoing investigations (428). The measurement of configural processing of objects is inferred through the use of hierarchical form tasks such as Navon Letters and illusions such as the Thatcher Illusion and the measurement of configural processing of face stimuli tends to be deduced by the existence of an inversion effect or the existence of an alignment effect when upper and lower face halves are misaligned. There needs to be a greater understanding of what constitutes configural processing, particularly, whether the configural processing required for faces and is the same as that required for global/ local processing of other objects and more object methods of measuring configural processing operationalised. Eye-tracking fMRI studies that interrogate attentional style are necessary to discriminate between reduced attention to the whole face and reduced attention to the features of the face such as the eyes. Previous studies of selective attention have found abnormalities in individuals with ASD and have suggested selective attention as a possible low-level mechanism for the high-order atypicalities in perceptual style in ASD (429). Eye-tracking during fMRI studies is necessary to determine the neural activation associated with preferential attention to eyes, rather than mouths, and activation associated with social rather than inanimate objects. Eye-tracking should also be used in future fMRI studies to explore if attention to the whole face and the configural processing of faces are actually overlapping constructs. Eye-tracking fMRI studies may help to determine why some studies have and others have not found fixation abnormalities in autistic children when shown faces percepts (215, 430). Unfortunately eye-tracking technology was not available at the point the data was collected for both the categorical and dimensional fMRI studies to determine the relationship between right FG activation, attention and configural processing in individuals with ASD. Eye-tracking is imperative to determine attentional patterns during configural processing in typically developing individuals and the development of fMRI goggle systems, which allow video monitoring of the corneal region with infrared illumination, offer the opportunity to undertake analysis informed by eye-tracking data. FMRI goggle system technology allows eye movement to be recorded dynamically and has the capability to record movements across time. The development of this technology allows for further experiments to address the outstanding attentional and configural processing questions highlighted in this thesis and would be well suited to address the apparent paradox of right FG hypo- and hyper-responsiveness in future studies. For example, the categorical experiments that found reduced right FG could be rerun and either (i.) eye-tracking data used post-processing to ensure that only data acquired when individuals were attending to the eyes is included in the analysis and/ or (ii.) the eye-tracker used to feed eye position information back into the video system and alter the location of image

presentation, so that the image always "moves" to fit the eye and the individual is in effect always attending to the eyes region of the face while right FG is measured. Measurement or control for fixation on features of the face would address previous limitations associated with interpretation of neural activation in the categorical and dimensional studies.

Other possible explanations for the task-dependant right FG hypo- and hyper-responsiveness in the categorical and dimensional studies require further consideration of the paradigms presented, and includes task-dependant differences in attention and/ or configural processing in the respective paradigms. Faces, when used in relatively simple visual tasks are consistently shown to activate the right FG gyrus. The complexity of facial expression processing in the DFEP attempts to simulate real life and goes beyond passive viewing or matching facial expression tasks. Attention to the whole face and/ or configural processing of the whole face during the DFEP in the SCD group might, therefore, be expected to be associated with increased activation in the right FG ROI in individuals with SCD. A recently published study of facial expressions processing reported that the fusiform and extrastriate cortices were shown to be activated by facial expressions of primary emotions in people with AS, but generally to a lesser degree than controls and researchers have been keen to related this to the social impairments of people with AS (431). However, this study did not measure attention to the face and individuals were asked to attribute sex of the individual in the photograph not emotion from the face of the individual. Interestingly, this study also reported increased FG activation in AS during the implicit processing of neutral faces presented as part of an experiment that measured brain activation to facial expressions of disgust. This finding provides evidence that individuals with ASD can demonstrate right FG hyper-responsiveness when processing face percepts and lends support to the right FG ROI finding in the non-inverted condition of the DFEP.

Possible explanations for the right FG hyper-responsiveness include that the dynamic facial expressions may have been more socially salient and, therefore, commanded increased attention in the high functioning group with SCD, which has been reported to result in increased right FG activation (238). Indeed, individuals with ASD have been reported to show higher activation during the passive viewing of facial expressions when the facial expression was varied compared to when the facial expression remained constant (259). Previous studies have also reported that when tasks incorporate biological movement, autistic children perform relatively adequately in emotional and non-emotional expression-recognition tasks when the facial expressions are displayed slowly on video (4). Individuals with developmental abnormalities are able to acquire face processing skills leading to intra-task variation in right FG activation between session (404). The development of expertise in individuals with ASD through training with novel percepts has also been related to greater activation of the right FG (242) as has developmental age (243). Dynamic facial expressions have been reported to facilitate attribution of emotion from facial expressions by facilitating configural processing (432). Brain regions implicated in processing facial affect, including the FG, showed greater responses to dynamic versus static emotional expressions highlighting the importance of temporal cues in the neural coding of facial displays (433). The use of dynamic facial expressions offers a possible explanation for the right FG hyper-responsiveness from the literature specific to face processing. In addition other fMRI studies of

individuals with ASD, such as a recent study of the neural basis of irony comprehension found that have found that children with ASD, who had difficulty interpreting the communicative intent of others, compensated by activating the neural circuitry involved in social processing to a greater extent than typically developing individuals (434). Indeed, there are other fMRI exemplars of individuals with ASD compensating with greater neural activation when a task is found to be difficult (435). These studies support the notion of right FG hyper-responsiveness to compensate for reduced expertise and achieve a successful performance in the non-inverted facial expressions condition of the DFEP in the proband group. One could also postulate that the right FG hyper-responsiveness is because the configural processing is necessitated, or that attention is required to the whole face. The explicit nature of the task (e.g. unhappy, happy and no change) may also have contributed to the right FG hyper-responsiveness during the attribution of emotion from facial expressions in the DFEP. Further development of the DFEP is needed such as the calculation of average expertise in typically developing individuals for each stimulus to determine the normative attribution point for comparison and used as the midpoint of stimulus presentation to remove "ceiling" effects. The use of a modified DFEP and eye-tracking technologies would help clarify the relationship between attention and configural processing in facial expressions processing in ASD. Indeed, attention and/ or configural processing may actually be dependent/ inter-related explanatory constructs for the right FG hypo- and hyper-responsiveness seen in the categorical and dimensional studies.

Previous eye-tracking studies have investigated percentage fixations on areas of the face, and found that individuals with ASD attend more to the mouth area of the face (205). Although, these studies have attempted to understand visual perceptual processes by recording eye movements, it has been unclear what you would measure to infer configural processing. Recently, it has been proposed that eye-tracking technologies can be used to measure the timing of attention fixations on the face and determine the occurrence of configural processing (437). This proposal is based on findings that suggest subjects can perceive certain patterns or elements in a pattern within 40 to 50 ms by means of an automatic or parallel process, referred to as pre-attentive search. Pre-attentive search is distributed over the whole image to allow patterns to be discriminated very rapidly over large areas. By contrast, attentive search requires longer scrutiny (>50 ms) of individual elements in the pattern and is carried out by a serial search process (436). Future studies might hypothesis that short eye movements of less than 50.1 ms would be involved in perceiving the face as a whole (facial configuration), whereas longer eye movements would be required to perceive individual facial features. Previous studies have suggested that right FG activation is task-/ condition-dependant with right FG hyper-responsiveness seen in tasks that require configural processing and hypo-responsiveness seen in tasks that do not required configural processing. This falls within the hypothesis based on pre-attentive and attentive search associated with the perception of the face as a whole (configural processing) and perception of individual facial features (part-based or component processing) respectively. Studies of face processing in other neurodevelopmental disorders confirm that pre-attentive search is involved in configural processing (323), whereas attentive search is involved in processing parts of the face. Therefore, further eye-tracking fMRI studies are required to test whether abnormal scanning of faces in individuals with SCI is related to the scanning of facial configurations or features. Potentially, these further studies offer a way to address the hypothesis that

right FG activation is task-/ condition-dependant with right FG hyper-responsiveness seen in tasks/ conditions that require configural processing and hypo-responsiveness seen in tasks/ conditions that do not required configural processing. Dynamic facial expressions could be presented in non-inverted and inverted orientations based on the previous assumptions that inverting faces distorts the integrity of internal features, thereby distorting the configuration formed by these features. The hypothesis would be that individuals with SCI would generate comparable number of saccades of 50.1 ms or less to controls in the tasks that required configural processing - EL task and non-inverted condition of the DFEP, and that individuals with SCI would generate significantly greater number of saccades of 50.1 ms or more than controls in the tasks/ conditions that did not necessitate configural processing such as the EM and inverted condition of the DFEP. Moreover, the individuals with SCI may have a greater number of saccades longer than 50.1 ms in tasks in explicit tasks as opposed to implicit emotion attribution tasks they use feature-based perceptual processing approaches.

The fMRI component is essential bearing in mind that comparable performance may be supported by atypical neural activation in individuals with ASD. Larger fMRI studies of expertise in the attribution of emotion should continue to investigate configural processing using different experimental fMRI designs. Conjunction analysis, an extension to cognitive subtraction, and factor analysis offer the potential to study CCI without the assumption of insertion inherent in cognitive subtraction. The neural correlates of the CCI in a conjunction analysis are defined by the activation differences common to task pair I and task pair II (438). In other words, cognitive subtraction identifies the activation differences between two task pairs that differ only by the CCI, and cognitive conjunction reveals the commonalities in activation differences between two pairs of tasks that share only the CCI. Conjunction analysis allows greater latitude in terms of selecting baseline tasks, because it is not necessary to control for all cognitive constructs other than the CCI and interactions that are not common to both task pairs are discounted. If the site of interactions is common to both task pairs, then a factorial design is required to allow the effect that one variable has on the expression of the other variable to be measured explicitly by calculating the main effects of each variable and the interaction between these variables. Factorial designs allow greater generalisation of the results because the level of effects can be specified for each factor (as in pure subtraction) or generalised for all factors. When the effect of one factor level varies according to the level of another factor, factorial designs allow us to verify the significance of this with the interaction term and importantly, factorial designs require fewer subjects for any fMRI study to achieve the same degree of power (438). However, all these experimental designs are based on subtraction logic. Future studies using parametric designs, which avoid the pitfalls of subtraction logic (406) are useful as they prevent the biases that can be introduced when the subjects perform different cognitive processes during the control and experimental task. Subjects are required to perform the same strategy less intensely in the control task, and more intensely in the experimental task, preventing biases introduced by differences in strategy between subjects and allowing investigation of the neural substrates related to increased load. The use of a parametric experimental design in further experiments would determine if increased right FG activation occurs in response to increased configural load by subtracting versions of the paradigm with different processing loads. Future paradigm designs that involve the use of static facial expression at different degrees of facial expression development taken from, for example, the DFEP movies could

be used to construct a parametric experiment. Future paradigm designs that involve the use of dynamic facial expression at different degrees of facial expression development taken from, for example, the DFEP movies could be also be used to construct a dynamic parametric experiment. Both these approaches would further interrogate if expertise in the attribution of emotion is related to the configural load inherent during face/ facial expression processing in individuals with ASD.

However, before claiming that the reduced pattern of a global advantage in autism is one of impaired configural processing, future studies need to rule out some alternative explanations. Several studies have suggested that spatial filters operate during the early visual processing (439) of global and local structures and that global advantage is mediated by low spatial frequency channels (324). Therefore, one possible explanation for the reduced ability to perceive the global form in hierarchical stimulus might concern a fundamental limitation in processing low spatial frequency information. Autistic individuals do perform poorly on tasks requiring face processing, including identity recognition as well as discrimination of gender, gaze direction and emotion (440), and it has been proposed that this is related to a fundamental limitation in processing low spatial frequency information. Future studies of spatial frequency are required to determine the overlap with configural processing and if this is a possible reason for faces processing deficits in high functioning individuals with ASD.

Other studies have reported that the use of dynamic stimuli may potentially confound the results of any study looking at configural processing (441). Therefore, in the dimensional study the contrasts were subtracted in such away as to remove activation related to biological motion. Although studies have argued for a low-level visual deficit in autism in the domain of motion perception this should not have had an effect in this study. However, given that individuals with autism have higher thresholds for motion detection than their peers (442), are deficient in motion direction discrimination (443) and experience difficulty with rapidly moving stimuli (416) when required to detect coherent motion while viewing random dot stereograms, it would be important to consider whether the use of biological motion might be confounding the experimental findings. Interestingly, these biases have been attributed to an alteration in the magnocellular pathways in autism (442), which could be reinterpreted as a higher-order difficulty in integrating local features, reflecting the same local bias as previously documented in autism. Thus, the deficit in biological motion detection might also arise from the failure to derive a global configuration from stimuli containing multiple local elements and further studies are needed to determine the overlap with configural processing in individuals with ASD.

Recent work suggests that other MRI methodologies are required to better interrogate the global local bias documented in ASD. Despite the popularity of WBA in SPM and ROI analysis, these methodologies do not directly explore the functional relationships between different brain regions, as SPM treats each voxel as an isolated entity (46) and ROI analysis treats each region as an isolated entity. Future studies that explore the functional relationships between different brain regions are needed to determine the neural underpinnings of atypical perceptual processing style/ strategy in individuals with SCI. As neurons in the brain have many connections to many other neurons and form neural networks of connected activity there is much interest in connectivity analysis in ASD. Emerging under-connectivity

theories recently proposed for autism suggest that the drive towards the processing of local information is secondary to the disconnection (444) or under-connectivity of the brain (445). Anatomically, there is evidence for both hyper- as well as hypo-connectivity in autism. During early development (between 7–11 years), white matter increases significantly more in autistic children than in normal children resulting in a transient hypertrophy of white matter (446), and this finding has later been complemented by results suggesting exaggerated pruning to subnormal levels, consistent with evidence for anatomical hypo-connectivity (445). As the categorical and dimension studies both showed atypicalities in neural activation in the right FG during face processing, further studies are required to investigate for differences in connectivity in neural networks related to face processing in ASD. A number of fMRI studies have supported the concept of reduced functional connectivity in autism in the frontal and parietal areas during an executive function task (447), during social cognition task (448), working memory task (449), visio-motor coordination task (450) supporting the notion that reduced functional connectivity may underlie a wide range of cognitive deficits in autism. Functional connectivity patterns that specifically relate to emotion attribution from facial expressions in typically developing individuals and individuals with SCI need to be identified. Functional maps can be used to create functional ROI that can be quantitatively compared between groups and to develop functional connectivity maps, which can be related to anatomical connectivity maps from diffusion tensor imaging (DTI). This comparison would give a comprehensive understanding of the connectivity of neural networks during emotion attribution from facial expressions in typically developing individuals and high functioning individuals with SCI.

However, MRI studies can only provide indirect evidence for abnormalities of structural and functional connectivity between cortical areas and electro-encephalography (EEG) and magneto-encephalography (MEG) are required to get sufficient temporal resolution to assess neural synchrony. A recent MEG study reported that ASD is associated with abnormal neural synchronization (451) and a study of face processing in autism found that controls had a differentiated response to face from no-face stimuli, while subjects with autism showed no difference between the two experimental conditions (452). EEG and MEG connectivity studies are needed to determine if there is reduced or otherwise abnormal synchrony during the DFEP. Research for abnormalities in temporal synchrony during the DFEP may be of relevance in determining the underlying causation of the right FG hypo- and hyper-responsiveness seen in these studies. The use of these advanced techniques for the identification of synchrony during complex cognitive tasks would clarify if the right FG hypo- and hyper-responsiveness is related to difference in neural asynchrony during feature-based and configural processing tasks.

During these investigations it should be borne in mind that brain connectivity is a developmental construct and that the brain regions responsible for face processing may be developmentally delayed or deviant in individuals with ASD. Review of the past studies shows that this developmental variability in acquisition of face processing is often not accounted for in study design. This developmental variability is demonstrated in the differing findings of studies of facial emotion processing in adults and children. Studies of children have found facial emotion processing difficulties (185), while studies of adults have found no facial emotion processing deficits (285). Some studies have not contained comparison groups (285), some have not matched the autism and comparison groups appropriately (275) and some have not

measured verbal ability or IQ. Future studies need to address these limitations and be cognisant of the different developmental stages of face processing while investigating for differences in patterns of activation and differences in both functional and anatomical connectivity in individuals with SCI.

11.2 Conclusions of the Categorical and Dimensional Studies

The categorical and dimensional studies of SCI were undertaken to explore behaviour, cognitive and functional levels of explanation for SCI, measured categorically as diagnosis of ASD and as a dimension of behaviour, to inform the development of an aetiologically valid integrated explanatory model for SCI. Individuals with ASD have been reported to use atypical perceptual processing strategies (316) and to have reduced (18) or absent right FG activation when viewing static face stimuli (6); therefore, previous fMRI research has focused on face processing deficits as a possible explanation for the SCI in ASD. However, recent fMRI research using static face percepts has reported comparable right FG activation to typically developing individuals when individuals with ASD attended to the eyes region of the face (9) and view the faces of familiar people (10). Consequently, face processing deficits and the associated reduced right FG specialisation for the processing of faces has become a contentious explanation for the SCI seen in autism. Another plausible explanation for SCI in ASD is reduced expertise in the attribution of emotion from facial expressions. Whilst reduced expertise in the attribution of emotion from facial expressions has been acknowledged as a potential explanations for the SCI in autism (1), there has been little research investigating deficits in facial expression processing as an explanation for the SCI in ASD (11) and the relationship with face processing *per se*.

Despite the task-dependant nature of the findings in these high functioning young men with ASD, the categorical studies did informed the development of a preliminary explanatory model for SCI in ASD. These studies provided preliminary evidence to support atypical perceptual processing during the attribution of emotion from facial expressions as a potential cognitive level explanation and reduced right FG as a potential functional level explanation for the SCI seen in ASD. The dimensional fMRI studies were undertaken to further explore reduced right FG specialisation for the configural processing of facial expressions as an explanation for SCI seen in ASD. However, paradoxically, the dimensional studies found an unexpected relationship between SCI, emotion attribution from facial expressions and right FG activation, which did not fit with the preliminary model for SCI. There was a relationship between SCI and right FG activation in both the non-inverted and inverted conditions of the DFEP; however, the hypothesis that SCI was related to reduced accuracy or response time during the attribution of emotion from dynamic facial expressions was not statistically supported. In the non-inverted task, SCI was related to increased accuracy, however, there was a trend in the proband group toward a significantly greater response time suggesting accuracy- speed trade-offs in the proband group. In the inverted task, there was a trend toward an indirect relationship between response time and SCI. The proband group also maintained comparable performance in the inverted condition of the DFEP, but used significantly less right FG activation than the brother group supporting the use of an alternative perceptual strategy in the proband group. This task/ condition-dependant atypical right FG hypo- and hyper-activation is suggestive of a predisposition toward an atypical perceptual processing strategy in individuals with ASD. Contrary to the notions of the failure of innate or experience-dependant right FG specialisation in autism

(1), based on the theories of Kanwisher (232) and Gauthier (240) respectively, both the categorical and dimensional studies support specialisation of the right FG in autism. However, it remains unclear if the capacity of right FG for the configural perceptual processing of face percepts is reduced and, consequentially, tasks that involve increased configural load problematic in the individuals with ASD or if there is a predisposition toward an atypical local processing style despite having the capacity to configurally process as previously reported in ASD (222). Alternatively, right FG activation may be a marker of attention to face percepts in ASD and right FG hyper-responsiveness reflective of the greater attention necessary to undertake configural processing when attributing emotion from dynamic developing facial expressions in young men with SCD. However, the same individuals did not use a right FG dependant processing strategy in the inverted condition of the DFEP when the task could be completed successfully without configural processing suggesting a predisposition toward atypical processing strategy in these individuals with SCI. Interestingly, these strategies were not associated with enhance perceptual processing in the ITG or left FG ROI as previously reported in ASD research (18); however, greater ITG activation was related to a faster response time in the inverted condition of the DFEP providing evidence that the greater the feature-based perceptual processing the faster the attribution of emotion from inverted facial expressions. This research provides evidence that individuals with SCI can configurally process face percepts, as previously proposed in the enhanced local perceptual processing theory (222) and the extended weak CC theory (411); however, does not support the use of enhanced local precedence supported in the ROI studied in the categorical and dimensional studies.

In conclusion, in terms of an integrated explanatory model for SCI, the categorical studies did informed the development of a preliminary explanatory model for SCI in ASD. The preliminary evidence from the categorical studies supported atypical perceptual processing during the attribution of emotion from facial expressions as a potential cognitive level explanation and reduced right FG as a potential functional level explanation for the SCI seen in ASD. The dimensional studies did find evidence for a relationship between SCI, measured as a behavioural dimension and right FG activation during the attribution of emotion from dynamic facial expressions, and implicated the right FG ROI, but not the ITG ROI, in an explanatory model for SCI seen in autism. The dimensionalisation of autistic symptomatology did facilitate behavioural, cognitive, and functional levels of investigation, and further investigation of SCI in high functioning young men with SCD. Indeed, the dimensional fMRI study provided further evidence of atypical perceptual processing in individuals with SCD, who all had SCI in the range previously seen in ASD (14). However, the direction of the relationship between right FG activation and SCI in the non-inverted and inverted conditions of the DFEP and the associated right FG activation differences were in the opposite direction to the hypotheses; therefore, the original hypotheses did not explained the SCI in ASD. Primarily this appears to be due to the use of an atypical task/ condition-dependant processing style in the proband group and further fMRI experiments are required to determine the task/ condition characteristics that relate to this atypical activation style before the reformulation of an explanatory model for SCI is tentatively proposed.

Both the categorical and dimensional studies provide evidence in support of the functional specialisation of the right FG for the configural processing of facial expressions and atypical task-dependent perceptual

processing in these high functioning individuals with SCI in both face and facial expressions processing paradigms. Differing configural processing and attentional demands inherent in the experimental paradigms and atypical perceptual strategies in individuals with SCI offer possible explanations for the right FG hypo- and hyper-responsiveness seen in these and other studies of face and facial expression processing in ASD. The categorical and dimensional studies in this thesis suggest that individuals with SCI are characterized by generalized atypical visual perceptual face processing, despite having the capacity to configurally process face and facial expression percepts. However, the degree of right FG specialisation and capacity to configurally process faces remains unclear and requires further study. Further studies are also required to further investigate accuracy-response time trade-offs and determine if high functioning individuals with SCI are less expert in the attribution of emotion from facial expressions. The relationships between SCI and expertise, and expertise and right FG ROI and the apparent paradox of the right FG hypo- and hyper-responsiveness in the categorical and dimensional studies need to be addressed in further studies as suggested in the previous section.

Although fMRI investigation of brain activation during the attribution of emotion from static and dynamic facial expressions in individuals with SCI did elucidate an aetiologically based correlate for SCI, the cognitive mechanism linking this brain activation to SCI needs to be further elucidated. FMRI studies that incorporate eye-tracking technology are needed to determine the relationship between right FG activation, configural processing, attention to faces and perceptual style in ASD. Future functional connectivity, MEG and EEG studies are necessary to study the integrity and synchrony of neural pathways involved in the attribution of emotion from facial expressions. Further fMRI studies utilising parametric experimental designs are required to determine if neural activation patterns related to increased configural load are typical or atypical in ASD.

Although the advent of such technologies are poised to inform our theoretical conceptions of these disorders, and facilitate research to determine underlying aetiologies of complex neurodevelopmental phenotypes (36), the categorical and dimensional studies highlight the complexity of studying developmental disorders when little is understood in terms of typical development (332). Continued use of integrated approaches to ASD research are important, as they force consideration of the ethological validity of constructs and ensure all levels of explanation constrain and inform each other (4, 5). Future integrative research will be facilitated by the further development of phenomics, the study of biologically valid constructs, in the next decade and the use of knowledge management systems to refine integrated hypothesis such as the hypothesis tackled in this thesis, and are briefly reviewed below.

11.3 Future Directions for Integrative Research

The future direction of integrated research at the behavioural, cognitive, functional, and genetic level will be determined by advances such as the development of phenomics, knowledge management systems, functional genomics, and genetic analysis. Conventional diagnostic boundaries based largely on behavioural symptoms, not only fail to reflect the underlying biological processes, but also prevent the discovery of basic mechanisms by reinforcing invalid distinctions. The identification of valid biological explanatory constructs involving the redefinition of phenotypes, and measurement across conventional

diagnostic boundaries, and even across species, is necessary. Brain imaging may not yet be reliable at the level of individual activation, however, neuroimaging tests that are informative at the individual level are likely to emerge in the near future (404). Further advances in fMRI will lead to the cognitive profiling of individuals, akin to a cognitive 'finger print', through the identification of patterns of activation related to informative cognitive tasks. These cognitive phenotypes will transform genetic analysis and the increase in data will require the development of phenomic knowledge databases. These phenomic knowledge databases will house phenotype catalogs with measures derived from behavioural, cognitive, functional, and genetic studies. The use of these knowledge management tools will allow the translation of phenotypic information across disorders and accelerate the discovery of genes for neurodevelopmental disorders.

This explosion of phenotypic knowledge will be matched by new genetic strategies influenced by the recent completion of a working draft of the human genome sequence. Knowledge of the human genome sequence promises to provide unprecedented opportunities to explore the genetic basis of individual differences in complex behaviours and vulnerability to neurodevelopmental disorder. FMRI, because of its unique ability to measure information processing at the level of brain function within individuals, provides for a powerful approach now termed functional genomics. Indeed, recent MRI studies have established important links between functional genetic polymorphisms and robust differences in information processing within distinct brain regions that have been linked to the manifestation of various disease states such as schizophrenia (453) and anxiety disorders (454). Importantly, all of these biological relationships have been revealed in relatively small samples of healthy volunteers, and interestingly, in the absence of observable differences at the level of behaviour and/ or cognitive explanation underscoring the potential of fMRI in exploring the functional impact of genetic variation (310).

Large-scale association studies using current diagnostic criteria followed by multivariate analyses, which include phenomic and environmental variables as well as genetic data, may fare better than traditional linkage analysis in disentangling the complex genetic disorders (455). Alternatively, candidate susceptibility loci, that is loci that have been linked with autism (456), can be used as a starting point for 'bottom up' gene identification. However, with this style of approach, it remains unclear what behavioural or cognitive features correspond to the possibly discrete inherited vulnerabilities (135). The search for an appropriate way to define phenotypes in order to enhance the discriminative capacity of linkage and association studies is increasingly recognised to be of crucial importance for understanding the genetic basis neurodevelopmental disorders (457, 458) and will most probably be addressed using increasingly sophisticated phenotypic tools to sub-divide and quantify the components of ASD into biologically valid dimensions. Strategies such as subdivision of ASD into cognitive and/ or functional endophenotypes are required in addition to the use of dimensional and categorical behavioural measurements. The development of quantitative phenotypic behavioural, cognitive and functional measurement techniques will enable the underlying genetic mechanisms to be interrogated using quantitative trait analysis and increase the power of future studies to detect underlying genetic susceptibility (459), and elucidate the biological underpinnings of SCI as seen in ASD.

Multiple explanatory levels need to be integrated to rectify the many gaps in knowledge that currently prevent us bridging between our clinical understanding of neurodevelopmental disorders and an understanding of these disorders, or dimensions of these disorders, at the aetiological level. Functional and anatomical MRI techniques, MEG and EEG are poised to revolutionise our understanding of brain function and development, but will not do so in isolation. Hypothesis-driven studies that integrate behavioural, cognitive, and functional levels of investigation are crucial to prevent an inappropriate focus on chance findings. Further integrative research (19) is required to identify robust cognitive and/ or functional level explanations for SCI. Ultimately, elucidation of the underlying aetiology of SCI will provide for biologically appropriate interventions at multiple levels of any integrated explanatory model developed for the SCI seen in ASD.

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Appendix 1: ICD-10 Diagnostic Criteria for Autism

A. Presence of abnormal or impaired development before the age of three years, in at least one out of the following areas:

1. Receptive or expressive language as used in social communication
2. The development of selective social attachments or of reciprocal social interaction
3. Functional or symbolic play

B. Qualitative abnormalities in reciprocal social interaction manifest in at least one of the following areas:

1. Failure adequately to use eye-to-eye gaze, facial expression, body posture and gesture to regulate social interaction.
2. Failure to develop (in a manner appropriate to mental age, and despite ample opportunities) peer relationships that involve mutual sharing of interests, activities and emotions.
3. A lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people's emotions; or lack of modulation of behaviour according to social context, or a weak integration of social, emotional and communicative behaviours.

C. Qualitative abnormalities of communication manifest in at least two of the following areas:

1. A delay in, or total lack of development of spoken language that is not accompanied by an attempt to compensate through the use of gesture or mime as alternative modes of communication
2. Relative failure to initiate or sustain conversational interchange in which there is reciprocal to and from responsiveness to communications of the other person
3. Stereotyped and repetitive language or idiosyncratic use of words or phrases
4. Abnormalities in pitch, stress, rate, rhythm and intonation of speech

D. Restricted repetitive, and stereotyped patterns of behaviour, interests and activities, manifest in at least two of the following areas:

1. An encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus; or one or more interests that are abnormal in their intensity and circumscribed nature although not abnormal in their content or focus.
2. Apparently compulsive adherence to specific, non-functional, routines or rituals
3. Stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting, or complex whole body movements
4. Preoccupations with part-objects or non-functional elements of play materials
5. Distress over changes in small non-functional, details of environment

E. The clinical picture is not attributable to other varieties of pervasive developmental disorder; specific developmental disorder of receptive language (F80.2) with secondary socio-emotional problems; reactive attachment disorder (F94.1) or disinhibited attachment disorder (F94.2); mental retardation (F70-72) with some associated emotional or behavioural disorder; schizophrenia (F20) of unusually early onset; and Rett's syndrome (F84.2).