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COGNITIVE PROCESSES IN EMOTION RECOGNITION: A PET STUDY OF MEN, WOMEN AND ADULTS WITH AUTISM

By

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Abstract

We were interested in localizing the regionally specific brain responses which underlie the emotion processing strategies of men, women and a clinical population of individuals with emotion processing deficits: autism. In two studies we identified the brain regions involved in the recognition of emotion by measuring changes in regional cerebral blood flow (rCBF) using positron tomography. Study I asked adult men and women to perform face detection, identity matching and emotion matching tasks and compared the distribution of rCBF produced by each task. The recognition of facial emotion by males was associated with activation of the right inferior frontal cortex, whereas in females, activation of the frontal cortices bilaterally, and the right middle temporal and right inferior occipital gyri was identified. Between-group comparisons of the activations associated with facial emotion processing revealed that males showed greater right sided activation of medial frontal and superior occipital regions and less activation of the left inferior frontal gyrus, left fusiform gyrus and right amygdala than did women. Localization of function to these regions is consistent with other research results identifying greater distribution and less lateralization of cognitive functions in females than males.

In our second study we presented cross-modal (auditory-visual) gender matching and emotion matching tasks to three groups of adults; men, women, and high functioning men with autism. Compared to the gender matching task, emotion matching was associated with activation of a left inferior frontal region in males, and the right superior temporal gyrus and right anterior cingulate gyrus in females. This pattern was similarly reflected in between-group comparisons, which identified significantly greater activations in a left inferior frontal region for males, and greater anterior cingulate and fusiform activations for females. These results identify sex differences in cross-modal emotion processing. Localization to these regions

suggests that females placed greater relative processing emphasis on the auditory-prosodic and motivational qualities of the current experience, whereas males relied more on processes engaged in the construction of an integrated emotional experience and the regulation of responses.

Cross-modal emotion matching by adults with autism was associated with activation of Broca's region, and bilateral anterior temporal poles. Between-group comparisons identified significantly greater activation of the right anterior temporal pole and anterior cingulate by the adults with autism, as compared to controls. These findings suggest that the adults with autism placed greater emphasis on processes involved in accessing perceptual knowledge to guide the categorization of emotional stimuli, verbal problem solving, directing attention toward cross-modal information sources and / or assessing the motivational content of stimuli.

Dedication

I dedicate this thesis to my adoring wife, Audrey and my children, Brian and Brittany
for all their love, support, patience and encouragement.
They have made this time in my life richly rewarding and truly wonderful.

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Introduction

The great strength of functional imaging lies in its capacity to localize functionally related regions of neural activity which underlie cognitive and emotional processes. In recent years these methods have been used in normal participants and increasingly in patients with neurological and psychiatric disorders. With each clinical population studied, experimenters face new challenges in the design and refinement of cognitive tasks, experimental conditions and imaging. However, with these challenges come new opportunities to build on existing knowledge, and explore the neurocognitive complexities of each disorder. Ultimately, it is hoped that such information will lead to improvements in the treatment and remediation of these disorders.

This thesis details our process of discovery. We wished to identify the neurological substrata underlying the deficits in emotion processing characteristic of individuals with autism. To date, few functional studies of autism have been conducted, and until recently, none have directly examined the question of emotion processing. However, the population distribution of autism shows a strong gender bias, with males being 4 times as likely to develop the syndrome. Although evidence exists identifying sex differences in the localization and/or functional distribution of some cognitive capacities in men and women, functional imaging research in normal adults has not directly examined the question of whether men and women use the same strategy for the recognition of emotion, or whether each use a gender specific strategy. We drew on the methods developed in previous published work in this area and studied emotion processing in a group of young adult males and females. This experience provided us with the

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opportunity to further refine our emotion tasks, consolidate our experimental protocol and incorporate procedures that would facilitate the study of adults with autism. Our second study, then, examined a group of high functioning adults with autism. This study also examined a group of young adult males and females, in order to extend the research on sex differences in emotion processing.

The chapters in thesis are organized to provide the relevant background to autism, sex differences in emotion processing and positron tomography, and, subsequently, to present the findings from our two studies. The first chapter provides an overview of autism, examines the social deficits of this syndrome within a developmental framework, and reviews the evidence of neurological dysfunction in autism identified through morphological and functional imaging studies. In Chapter Two, the neurofunctional mechanisms of facial emotion processing are examined and evidence of sex specific strategies in emotion processing is presented. Chapter Three covers the positron tomograph, functional imaging, and the scan procedures and image analysis methods used in the studies of this thesis. Chapter Four outlines the experimental task and protocol, and the results from our first study of visual emotion processing in two groups: normal adult males and normal adult females. In Chapter Five, the protocol for our second study is presented, and the results for a group of normal adult males and a group of normal adult females are reported. In Chapter Six, the results for a group of high functioning adults with autism are presented. For comparison, the results from our normal male (control) participants are briefly summarized. In Chapter Seven the data from both studies are examined using Random Effects analyses, and group differences are discussed. Finally, in the last chapter, a number of future directions for this research are discussed.

CHAPTER ONE

1.1 OVERVIEW OF AUTISM

Autism is a developmental disorder manifest in disabilities that extend over a lifetime. It may be identified in infancy as impaired attachment, but is more often detected in toddlers between 18 and 30 months of age, when parents or professionals observe an absence or delay in speech and limited social interaction. Autism is defined behaviorally by a triad of impairments in social reciprocity, imagination and verbal and nonverbal communication, and by the presence of repetitive or ritualistic behaviors (Denckla, 1986; Wing, 1981). In general, the principal characteristics supporting a diagnosis of autism include (Damasio and Maurer, 1978; Sigman, Arbelle and Dissanayake, 1995):

a) failure to develop normal social relationships; including deficits in reciprocal social interactions such as social referencing, joint attention, emotional sharing, greeting behaviours, offering and seeking comfort, and the development of close friendships.

b) developmental disturbances of verbal and nonverbal communication; as many as one third to one half of people with autism are without speech. In those with speech, it is characteristically abnormal in terms of amount, content, grammatical structure, and social usage, and includes idiosyncratic language, echolalia and stereotyped utterances. (Frith and Happe, 1994; Wing and Gould, 1979). In some high functioning individuals with autism verbal ability can be relatively normal except for unusual concreteness and dysprosody. Deficits occur in all forms of nonverbal communication including gesture, facial expression, and posture.

c) repetitive, restricted and stereotyped behaviours; including resistance to change in routine

or surroundings, unusual preoccupations, abnormal attachments, rituals, compulsive

behaviours and unusual sensory interests.

d) disturbances in motility; including stereotyped movements, abnormalities of gait and

posture and emotionally linked facial asymmetry.

Autism is often accompanied by mental retardation, with the majority of individuals

showing evidence of cognitive impairment and only 20-25% scoring within normal or near

normal ranges on standardized tests of intelligence (Bryson, Clark and Smith., 1988; Freeman et

al., 1985). However, cognitive level is not a defining feature of autism, and, even though it has

a marked effect on the expression of symptoms (Rutter, Greenfeld and Lockyer, 1967), it is the

failure to acquire adaptive functional behaviors that distinguishes individuals with autism from

other developmentally disabled groups (Jacobson and Ackerman, 1990) and prevents them

from functioning independently in society (Bryson,1991).

The syndrome was first defined 1943 by Leo Kanner, in a description of a group of

eleven children that shared a similar set of unusual characteristics. He emphasized the

interpersonal deficits of these children and the "extreme autistic aloneness" that served to

block out the external world (Kanner, 1973; pg 33). The early descriptions by Kanner were very

thorough and in many ways remain congruent with the current criteria used to define autism.

However, in recent years the concept of autism has broadened and the newly coined terms

Autism Spectrum Disorder and Pervasive Developmental Disorder (PDD) have signified the

recognition that some children possess many, but not all of the characteristics of "classic" or

Kanner autism. In the current model, children with the triad of impairments associated with

autism differ clinically from one another in the degree of impairment exhibited and there are

no clear boundaries distinguishing the diagnostic categories across the spectrum.

In addition to classic autism, the most recent revision of the diagnostic manual of the

American Psychiatric Association (DSM IV, 1994) lists four further PDD subtypes;

Retts Syndrome, Childhood Disintegrative Disorder, Asperger's Syndrome and Pervasive

Developmental Disorder - Not Otherwise Specified (PDD-NOS). Rett Syndrome is found primarily

in females, where there is an apparently normal pre- and perinatal development, and an onset

of symptoms after the age of 5 months. In addition to other recognized features of autism,

females with Rett Syndrome demonstrate decelerated head growth, a loss of purposeful hand

movements (hand wringing), and psychomotor retardation. Childhood Disintegrative Disorder or

Heller's syndrome is seen in children where development proceeds normally for several years,

with the acquisition of age appropriate social skills, imaginative play and communication.

Some time after the age of 2 years there is a marked regression in skills in multiple areas and

the development of various features of autism. Children with Asperger's syndrome do not

suffer from the deviant language acquisition and complete social isolation seen in autism;

rather, they may demonstrate pedantic speech, social ineptness, egocentrism and restricted,

eccentric interests. Finally, children diagnosed with PDD-NOS are seen to have many autistic

characteristics, but insufficient in sum for a full diagnosis of autism.

1.1.1. EPIDEMIOLOGY

At present, autism remains one of the most reliable clinical diagnoses in psychiatric and

developmental research (Bristol et al., 1996). Estimates of the frequency of autism in the

general population are reported at 1 per 1000 and the ratio of males to females is generally

3 or 4 to 1 (Bryson, Clark and Smith, 1988; Bryson, 1996). Recent estimates of the broader

diagnostic syndrome produce a higher frequency of 2 per 1000 (Honda et al., 1996; Wing, 1991).

These prevalence values are on par with those reported for both Down Syndrome (1.3/1,000;

Zarfas and Wolf, 1979) and congenital deafness (1 to 1.5/1,000; Parving, 1999).

1.1.2. ETIOLOGY

The specific etiology of autism remains a mystery. However, there is general

agreement that autism results from a biological disruption of the developing fetal brain

structures that are ultimately responsible for socialization, communication and play.

Neuroanatomical accounts of autism have most often implicated the brain stem, the

cerebellum, the limbic system and selected areas of the cerebral cortex (Damasio and Maurer,

1978). Brain stem theories have focussed on deficits in attention and arousal, while cortical

models have stressed deficits in information processing (Ornitz, 1989; Ozonoff, Pennington and

Rogers, 1991). Recent formulations have highlighted the interaction of all or most of these

areas and changes in the rich interconnections that normally bridge them (Rodier et al., 1996;

Rodier, 2000). However, as yet, there is no unifying theory or explanation that can account for

the wide variety of symptoms in autism.

Attention has also focussed on converging evidence that genetics play an important,

though not exclusive role in the etiology of autism (Szatmari, 1996; Piven and Folstein, 1994).

The precise mode of transmission is complex and most likely the result of mechanisms that

involve more than a single major locus. In families with one affected child there is a 3 to 8

percent chance of recurrence. The likelihood that same sex dizygotic twins are both diagnosed

with autism is between 5 and 10 percent, while monozygotic twins carry a much higher

concordance rate of 90 percent (Bailey et al., 1995). Furthermore, a set of monozygotic twins

may not be equally affected, and it is this variation in the phenotypic expression and the high concordance rate that indicates that the syndrome is produced by an interaction of non-genetic factors with the expression of one or more genes (Rapin, 1997). Research continues to tease apart the impact of familial and environmental factors on individuals with increased genetic vulnerability to the syndrome.

In the vast majority of cases there is no identifiable medical reason for autism. There are, however, a number of medical/genetic disorders that affect the developing central nervous system and have, in some individuals, been observed in conjunction with autism. The two disorders with the strongest association to autism are Fragile X syndrome and tuberous sclerosis (Gillberg and Coleman, 1996; Hunt and Shepherd, 1993). In addition, autism has been reported in individuals with rubella embryopathy (Chess, 1971), phenylketonuria, (Friedman, 1969) and a number of other medical conditions (see, for example: Gillberg and Coleman, 1996). Still, it has been estimated that these disorders are present in only 17% of all individuals with autism and in 27% of those from the broader autistic spectrum (Wing and Gould, 1979). Presumably, there is a similar neurological substrate that can account for the behavioral features shared among individuals with autism with an unspecified etiology and those with an associated medical disorder. However, there is a trend for the rate of associated medical disorders to go up with lower IQ in individuals with autism, raising the possibility that the autistic symptomatology is an expression of non-specific mental retardation (Szatmari, 1996).

1.1.3. INTERVENTION

At present there is no drug or other treatment that cures autism. Medication may be employed to target specific symptoms, for example serotonergic antidepressants may be prescribed to control stereotypies, perseveration and mood swings (Bauer, 1995). However, many children with autism do not require medication. Currently, the most important intervention in autism is early and intensive individual instruction that addresses the social, behavioral and communication needs of the child.

1.1.4. COURSE AND PROGNOSIS

The nature of the social and communicative abnormalities in autism tend to change as the child develops. The most severe problems are evident in the preschool years when there is a marked delay in the development of specific attachment behaviors and abnormalities in verbal communication and nonverbal interaction (Rapin, 1991). Abnormal eye gaze, for example, is characteristic and the initiation and response to physical contact also tends to be abnormal (Sigman, Arbelle and Dissanayake, 1995). Beyond the age of 5 years, these grosser abnormalities become less evident as children develop an ability to communicate their needs and influence people. Nevertheless problems in social functioning remain, including impairments in social reciprocity, a lack of cooperative play, restricted interests, a failure to develop personal friendships, a lack of empathy toward the feelings of others and a general inability to coordinate behavior to signify social intent (Lord, 1984). As adults, few individuals with autism achieve independence. They often require assistance in obtaining and maintaining meaningful work and in finding supportive living arrangements when they are no longer able to live at home. Adults with adequate social skills may be fortunate enough to find a specialized niche that enables them to become self reliant (Bryson, 1991).

1.1.5. CLINICAL PRESENTATION

Based largely on clinical experience, a classification scheme of autism has been

developed by Wing and Gould, (1979) that examines the quality of social interaction in order to

distinguish between three subgroups of autism. The subgroups, reflecting the social

disturbance characteristic of each, are aptly entitled: Aloof, Passive, and Active-but-odd.

Aloof individuals are identified by the absence of spontaneous social approaches to others and

a tendency to reject social or physical contact. Similarly, Passive individuals rarely engage in

spontaneous social approaches, however, they will participate in social interactions that are

initiated and structured by others. Finally, "Active-but-odd" individuals with autism do make

social approaches toward others, however they do so in a typically naive, peculiar or one-sided

manner. Wing and Gould (1979) suggest that there are specific patterns of behavior in each of

these subdomains that are particular to each group. For example, Aloof individuals typically

show impaired symbolic play and imitation, an insistence upon sameness and routines and poor

receptive and expressive verbal skills (Castelloe and Dawson, 1993). All three subgroups may

be recognized in one and the same child at different ages (Wing, 1981), with the progression,

and corresponding reduction in symptom severity, beginning with the Aloof subtype and ending

with the Active-but-odd subtype.

1.2 SOCIALIZATION

Understanding that autism originates with the disruption of prenatal neurodevelopment

has implications for a discussion of the social deficits associated with the syndrome.

Social-cognitive capacities emerge throughout normal development and are the product of an

interplay between new social experiences and the developing nervous system (Karmiloff-Smith

et al., 1995). At various stages, emergent social capacities may be deficient in autism and their expression and progression are a function of the underlying blockades and distortions in development and the adaptations and compensations that have taken place along the way.

A recurrent debate in autism research concerns the identification of a primary deficit from which the full range of symptoms can be accounted. The search for a primary deficit is driven partially by the notion that such a framework could be employed to guide treatment. A deficit can be considered primary if it is specific to individuals with autism, is consistently identified across the full spectrum of autism and takes causal precedence in development (Ozonoff et al., 1991). Efforts to identify a single core deficit in autism have often failed to employ a neurodevelopmental framework, and therefore in the face of evidence that some members of the population are able to perform a certain social function, the disability is dismissed as the likely "core" deficit. A more productive approach would be to entertain multiple primary deficits, each one considered a "core" deficit as it is mapped onto the current emergent capacities of the nervous system or regard all as part of a larger deficit in socialization. If we examine the literature on autism from this perspective, we find at least four socialization deficits that follow a developmental progression in their acquisition. These are reciprocity, joint attention, the perception and understanding of emotion, and theory-of-mind. These deficits are acquired in sequence such that the development in one area impacts on all others that follow.

1.2.1. RECIPROCITY

With normal development, a remarkable achievement occurs near the end of the first year of life when an infant looks to the face of another person for their reaction to an amusing, interesting or startling event. These beginnings of social interchange occur as eyes meet and

for a moment both parties cooperate in a sharing of psychological space. In autism there is a

disturbance in the reciprocal quality of eye contact between the child and another person.

In fact this isolation and lack of social relatedness is a hallmark of the syndrome. Mutual eye

gaze is thought to be important in early attachment, and a necessary precursor to later social

understanding (Sigman, Arbelle and Dissanayake, 1995; Rogers and Pennington, 1991).

Deficits in social reciprocity continue to be observed after the age of five years in

autism. Children with autism are often unresponsive to peers, demonstrate difficulty judging

appropriate social distance, demonstrate a lack of empathy, have difficulties engaging in

cooperative play and fail to make personal friendships (Bauer, 1995). Instead, they spend

unusual amounts of time either unoccupied or engaged in ritualistic or repetitive activities

(Lord, 1984; Rapin, 1991).

1.2.2. JOINT ATTENTION

As development progresses, the normal 9 -14 month old infant engages in gaze

monitoring, by turning to follow an adult's line of sight and examine the same object or event

(Scaife and Bruner, 1975). Protodeclarative pointing emerges at about the same time, when

the infant points to an object with the sole purpose of directing another person to look at it.

Both protodeclarative pointing and gaze monitoring are forms of joint attention because they

result in the convergence of adult and infant attention onto the same object or event.

An analysis of first birthday home videotapes has found that relative to normal peers, children

with autism engage in less social and joint attention behaviors such as looking at the face of

another, seeking contact, pointing and showing (Osterling and Dawson, 1994). At this age,

children with autism are also distinguished from normal developing and Down syndrome children by poor visual orientation to social stimuli, delayed responses to being called by name, excessive mouthing of objects and an aversion to social touch (Dawson et al., 1998; Baranek, 1999). The absence of joint attention behaviors at 18 months of age, accompanied by deficits in pretend play, is highly predictive of a later diagnosis of autism at 3 years of age (Baron-Cohen et al., 1996). Furthermore, these joint attention deficits persist and are found in school age children with autism (Wing, 1976).

Protodeclarative pointing also permits the child to engage in an exchange with an adult in the absence of language, and may contribute to a deeper understanding of the signal value of gestures. At a young age, children with autism tend not to shake their head to indicate yes or no, use hand gestures to augment speech, or point to objects with the purpose of sharing (Loveland and Landry, 1986). The lack of these non-verbal behaviors can provide some of the earliest evidence that a child has autism (Baron-Cohen et al., 1996).

Natural opportunities for language development occur in infancy as parents label objects or events verbally for their child. The adult characteristically engages in a monologue that is very expressive, repetitive, and spoken in high tones. Failures to follow an adult's line of sight, and use eye contact and facial expressions to disambiguate the adult's reference (Philips et al., 1992), may reduce the opportunity for language development in autism. Failures to link an object with its label correctly can lead to idiosyncratic language use. Also common in autism are neologisms (newly created words) and familiar words that acquire special meanings, reflecting a concrete association of words and objects (Frith and Happe, 1994). The failure of joint attention in infancy and early childhood is also associated with difficulties with "I" and "you" pronoun use and thus contributes to a broader failure in social

language use (pragmatics, Loveland and Landry, 1986).

It has been suggested that the failure of the child with autism to engage in joint attention behaviours at a young age compromises the development of later social and cognitive capacities (Mundy, 1995). For example, joint attention may provide young children with an opportunity to compare their own emotional experience of an event with their perception of the emotional display of others who are engaged in viewing the same event (Mundy, 1995). Failures in joint attention may limit the opportunities for a child with autism to develop a conceptualization of emotion, and may account for the difficulties these children have recognizing facial emotion (Hobson et al., 1988a).

1.2.3. DISPLAYS OF EMOTION

Clinical observations suggest that children with autism rarely convey emotion through facial expression (Rutter and Lockyer, 1967). Behavioral recordings of children with autism between the age of 2 and 4 years in a naturalistic setting have identified that they display certain emotions less frequently than normal peers (happiness, surprise, anger) and are more limited and variable in their affective responses to adults (Trad et al., 1993). In addition, relative to controls, less frequent displays of positive emotions have been observed in children with autism in certain social contexts (Dawson et al., 1990; Kasari et al., 1990; Snow et al., 1987). Children with autism are less likely to share positive affect (by combining eye contact with the display of positive emotion) with other people than either developmentally delayed or normal controls and demonstrate difficulty when required to analyze emotional cues (see Trad, et al., 1993; Langdell, 1978; Kasari et al., 1990). When children with autism do display positive affect, it has been more highly correlated with self absorbed activity than with other-directed

activity (Snow, et al., 1987), suggesting that social experiences are not as intrinsically rewarding for children with autism. Finally, it has been observed that the faces of children with autism display significantly more incongruous blends of emotion (such as anger and enjoyment together), such that the social value of their facial expressions is reduced (Kasari et al., 1986).

1.2.4. PERCEIVING FACE EMOTION

It has been well established that faces hold special significance for the normal developing child. Infants, as young as one month of age are especially attentive to the complexity, animation and configuration of the human face (Sherrod, 1981). At three or four months of age infants fixate longer on smiling faces, than non-smiling faces (LaBarbera et al., 1976). Around one year of age infants react differently to a visual cliff, according to the emotional expressions they see on the faces of their watching mothers (Klinnert et al., 1983). Even at this early age, infants engage in social referencing (joint attention) and use the information from their mother's facial expressions to modify their behavior. At 2 years of age many toddlers are able to decode facial expressions and apply emotional labels to them; however they do not make inferences about the corresponding internal states of the person. By 3 years of age, the child has acquired a "desire-belief" psychology (Astington, 1988) and facial expressions are associated with a person's internal state.

There have been a number of studies that have attempted to relate the social impairments in autism to deficits in processing emotional cues (Hobson and Lee, 1989; Dawson and Fernald, 1987). Sigman et al. (1992) examined the responses of young children with autism

to the negative emotions of others. Under contrived circumstances, normal and mentally retarded controls were very attentive to adults who showed fear, distress or discomfort, while children with autism were less attentive and empathetic. Further, the responses of children with autism to displays of positive affect appear equally muted. It has been observed that in comparison to controls, children with autism responded less to praise from their mothers upon the successful completion of a puzzle (Kasari et al., 1993). In fact some of these children were observed to turn away or physically withdraw when praised. Undoubtedly, impairments in the processing of affective cues would lead to poor social relationships. Recently, Hauk et al. (1995) have provided evidence that connects emotion perception abilities in children with autism with poor socialization. They found a positive correlation between poor performance on affect and situation matching tasks and a reduced frequency of social initiations made by children with autism in a naturalistic play setting.

Weeks and Hobson (1987) observed that while normal controls sorted emotionally varied facial photographs according to facial expression, children and adolescents with autism tended to sort according to some non-social dimension such as type of hat. Braverman et al. (1989) found that children with autism were able to match pairs of photographs of both familiar objects and faces. However, these same children demonstrated impaired performances, relative to controls, in matching the emotional affect in photographs of faces. Moreover, evidence that individuals with autism are quite capable of recognizing people's identity by their facial features (Langdell, 1978; Hobson Ouston and Lee, 1988a) suggests that they do not have difficulty in judging complex facial configurations and that it is the recognition of emotion that is impaired.

Hobson, Ouston and Lee (1988a) found that the performance of an emotion sorting task by a group of mentally handicapped adolescents and young adults with autism deteriorated far more rapidly than that of matched controls when elements of the photograph (eyebrows, mouth) were blanked out. It was suggested that the paricipants with autism in this study had relied more heavily on elements of the face in order to complete the matching task, and therefore, when these elements were removed, their performances fell (Hobson, Ouston and Lee, 1988a). Similarly, higher functioning children and adolescents with autism, have been observed to use a more perceptually driven matching strategy while engaged in an emotion matching task (Ozonoff, Pennington and Rogers, 1991). In this study the participants with autism committed significantly more errors than controls in matching both simple (happiness, sadness, fear and anger) and complex emotions (surprise, shame, disgust, interest and contempt).

Capps, Yirmiya and Sigman (1992) found that around 12 years of age, higher functioning children with autism appear to use effortful cognitive strategies based on learned associations, rules, and prototypical references to label affect expressions and recount examples of emotions (Capps, Yirmiya and Sigman, 1992). Although photographs depicting simple emotions (happiness and sadness) were correctly labelled by their participants with autism, more complex emotions like pride and embarrassment were mislabelled and misattributed (Capps, Yirmiya and Sigman, 1992). In addition, the participants with autism in this study failed to include references about an audience when re-counting personal experiences of embarrassment. Capps and colleagues (1992) suggested that such responses were reflective of deficits in joint attention and affective sharing and evidence of a disturbance in the conceptualization and experience of emotion in autism. Taken together, these findings are important because they identify the use of less effective emotion processing strategies which extend across age and functional cognitive levels in autism. Furthermore, it has been

identified that emotion processing difficulties are correlated with the severity of symptoms in children with autism (Dawson and Fernald, 1987).

Some studies have demonstrated that differences in the performance of affect recognition tasks may be reduced when participants with autism are matched with controls on the basis of language ability (Fein et al., 1992; Hobson, et al., 1988a; Ozonoff, Pennington and Rogers, 1990), or full scale IQ (Capps Yirmiya and Sigman, 1992). It should be noted that research concerning normal child development has identified that gradual improvement in affect perception occurs between the ages of 2 to 12 years (Gross and Ballif, 1991). In view of the fact that children with autism usually perform more poorly on verbal than nonverbal tests (Prior, 1979), the end-result of matching participants on the basis of verbal skills would be to select a younger, developmentally less able control group. In fact, in one of the studies listed above (Ozonoff, Pennington and Rogers, 1990) the mean age of controls was three years (in contrast to a mean age of 6.4 years for the group with autism), likely an age when emotion recognition skills are beginning to be acquired (Gross and Ballif, 1991). It should come as no surprise, then, to find that the difference between the emotion matching performances of individuals with autism and controls is reduced when groups are matched on measures of verbal IQ. Furthermore, it may be suggested that the process of emotion recognition carries a strong visual perceptual demand (Tucker, 1981) and a more appropriate matching process would use non-verbal measures (Hobson, 1991). In all, the studies employing verbally matched controls do suggest that the degree of impairment in emotion recognition in autism is at least as severe as the disturbance in language development.

1.2.5 CROSS-MODAL PROCESSING

The emotional state of another person can be inferred from information acquired from a number of sources, including visual, auditory, gestural and contextual origins. The prosodic elements of speech can convey the emotion of the speaker. The ability to label vocal expressions of emotion has been shown to be impaired in autism (Hobson, Ouston and Lee, 1989). Even high functioning adults with autism demonstrate impaired performances in recognizing emotional speech and naming emotions relative to normal adult controls (MacDonald, et al., 1989). It may be suggested that, in autism, the combination of these difficulties with poor visual emotion recognition, would reduce the opportunity to develop learned associations linking the various modes of emotional display. In this regard, Hobson, Ouston and Lee (1988b) observed that adolescents and adults with autism have greater difficulty than normal controls in matching emotionally expressive faces, voices and gestures with each other. These difficulties could also arise from failures to integrate information arriving from different modalities. A number of studies have examined the ability of children with autism to match facial expressions to vocal affect (Hobson, Ouston and Lee, 1988b; Ozonoff, Pennington and Rogers, 1990; Van Lancker, Cornelius and Krieman, 1989). In each of these cross-modal studies voice/face affect matching was found to be impaired in individuals with autism. Thus it appears that individuals with autism not only display difficulties in discriminating facial emotion, but demonstrate further impairment when asked to process emotional cues arriving from more than one sensory modality. Furthermore, it appears that these difficulties persist into adulthood.

1.2.6 THEORY-OF-MIND

In autism, failures to engage in social-emotional sharing, and reciprocal interchanges may also impede the development of an appreciation that it is possible for others to have thoughts and feelings that differ from one's own (Mundy,1995). The use of such knowledge to rationalize and predict the behavior of others has been called the "theory-of-mind" (Baron-Cohen, Leslie and Frith, 1985). Many children with autism (more than 80% of those tested) fail on theory-of-mind tasks that are correctly completed with ease by matched controls (Baron-Cohen, Leslie and Frith, 1985). Happe (1991) observed that high functioning adults with autism may succeed at theory-of-mind tasks, and yet fail to use mental state inferences in their daily lives. This failure to explain and predict the behaviors of others can lead to further difficulties in understanding how another person can develop a false belief, or how another person can have knowledge of events that differ from one's own, or in understanding the social circumstances surrounding an act of deception (Happe, 1994). In addition, research has shown that the relative ability, or inability, of children with autism to take the perspective of another person is strongly correlated with their social functioning (Dawson and Fernald, 1987).

It has been suggested that deficits in theory-of-mind can account for many of the symptoms of autism (Baron-Cohen, 1988) such as impairments in social understanding, shared attention, empathy and pretend play (Leslie, 1987; Frith, 1989; Ozonoff, Pennington and Rogers, 1991; Capps, Yirmiya and Sigman, 1992). Some theorists have argued that an impairment in the acquisition of a theory-of-mind is the primary underlying deficit in autism (Baron-Cohen, 1988; Ozonoff and Miller, 1995) while others have emphasized the primacy of emotional processing deficits (Hobson, 1991). Developmentally, the acquisition of theory-of-mind is subsequent to that of joint attention and emotion recognition skills. In normal

children, the capacity to solve simple theory-of-mind problems is achieved around $3^1/_2$ to 4 years of age (Karmiloff-Smith et al., 1995). The arguments that pit emotion recognition against theory-of-mind as the core deficit in autism are moot, as both processes are inextricably connected in child development; understanding the complexities of emotions helps to build new mentalizing abilities and in turn, new found mentalizing skills deepen emotional awareness and understanding (Hobson, 1991; Buitelaar and vanderWees, 1997; Ozonoff, Pennington and Rogers, 1991). A more unifying position recognizes that both reflect the larger social deficit that defines autism.

1.3   NEUROLOGICAL EVIDENCE

Presently there exists a large body of literature describing a wide variety of neural abnormalities in autism. However, as yet, no coherent anatomical or pathophysiological theory of autism has been developed and theorists have focused on a number of neurological structures and systems including the brain stem (Ornitz, 1989; Rodier, 2000); cerebellum, (Courchesne et al., 1994); medial temporal lobe and amygdala (Damasio and Maurer, 1978; Bachevalier and Merjanian, 1994); frontal and temporal cortices (Horwitz and Rumsey, 1994; Ozonoff, Pennington and Rogers, 1991); or some combination of all or many of these regions (Waterhouse, Fein and Modahl, 1996).

Much of the evidence of a neuropathological foundation to autism had been derived from neuroimaging studies. These studies are separable along two lines; morphological studies aimed at identifying anatomically observable changes in the shape or size of structures, and functional studies that examine the underlying metabolic processes (Goldberg, Szatmari and Nahmias, 1999).

1.3.1. MORPHOLOGICAL STUDIES

In primary autism, where screening has selected out cases of tuberous sclerosis, epilepsy or other co-morbid neuropathology, the majority of individuals present with no observable gross structural neurological abnormality on X-ray Computed Tomography (CT) (Prior et al., 1984). MR imaging studies identifying morphological cerebral abnormalities in individuals with autism have yielded widely discordant and poorly corroborated findings (Filipek, 1996; Goldberg, Szatmari and Nahmias, 1999). For example, abnormalities in individuals with autism have been identified in a number of different structures including the brain stem, the cerebellum (Courchesne, 1995), structures of the limbic system (Alward et al., 1999; Abell et al., 1999), the corpus callosum (Egaas, Courchesne and Saitoh, 1995; Piven et al., 1997) and the frontal and temporal regions of the cerebral cortex (Abell et al., 1999).

1.3.1.1. BRAIN SIZE

In contrast to the obvious lesions or atrophy seen in many neurological disorders, magnetic resonsonance imaging (MRI) of autism fails to show atrophy. In fact some individuals demonstrate increased brain volumes. A number of researchers have noted larger than average head circumferences and greater total brain volumes in some individuals with autism (Bailey et al., 1995; Piven et al., 1995; Fombonne et al., 1999). In normal brain development there is an early overgrowth of neurons which is followed by pruning during the first few years of life. It has been suggested that larger brain sizes in autism may therefore reflect reduced or altered pruning (Minshew, 1996). This view implies that autism is not a destructive, but a dysgenetic process. However, in the absence of evidence detailing consistent changes along specific

pathways, these changes cannot account for the specific set of behaviors associated with autism and likely translate into more global developmental problems in the brain.

1.3.1.2. BRAIN STEM

Presently it is impossible to draw conclusions from MRI research on the brain stem. Most studies have not matched study populations and have used either neurological or normal controls (Goldberg, Szatmari and Nahmias, 1999). In one study, Gaffney et al. (1988) reported smaller pons and total brainstem area on midsagittal MR images in a comparison of 13 individuals with autism and 35 unmatched neurological controls. Hashimoto et al. (1995) reported smaller midsagittal areas of the cerebellum and brainstem in 102 participants with autism ranging in age from 6 months to 20 years. The control group in this study was made up of patients being evaluated for headache / head injury and staff of the research facility and their siblings. School records and brief assessment indicated that the control participants were at least of average cognitive ability, whereas only 17 of the 102 participants with autism had IQS in the normal range. These findings stand in contrast to a report of no differences between the size of the pons in individuals with autism and controls in a study that used similar methods and unmatched controls (Hsu et al., 1991). In a study that matched 15 high functioning adults with autism with controls on the basis of age, gender and nonverbal IQ, Piven and colleagues (1992) reported that the midsagittal area of the pons, fourth ventricle and cerebellum was significantly enlarged in autism. One plausible explanation of these disparate findings may be related to the IQ of the participants tested, as smaller brain stem regions have been reported in individuals with autism of lower intelligence (Hashimoto et al., 1995). However this remains speculative, until adequate controls are studied.

Recently, Rodier and colleagues (1996, 2000) have advanced the hypothesis that the initiating injury in autism takes place around the time of neural tube closure in the third to fourth week of gestation, resulting in a disruption in the development of brain stem nuclei. These researchers drew on work demonstrating high incidences of autism in a select group of children born to mothers using thalidomide between the 20th and 24th day of gestation (Miller and Stromland, 1993). At autopsy, a single case of autism revealed a shortening of the brain stem, between the trapezoid body and the inferior olive, and a near-complete absence of the facial nucleus and superior olive. Rodier et al. (1996) proceeded to test an animal model in which they demonstrated a selective loss of neurons in brainstem nuclei of rats that had been exposed to valproic acid at the time of neural tube closure. The treated rats were otherwise robust and the valproic acid exposure did not produce grossly observable changes in the continued development of their brains.

The work by Rodier et al. (1996) is intriguing because it suggests that histological changes observed in other areas of the autistic brain, like the cerebellum or limbic system, may be secondary to early injury in the brainstem, and a result of progressive changes in neurodevelopment as these regions respond to abnormalities in their target cells, or to changes in their input. Furthermore, these researchers suggested that some of the symptoms of autism may be explained by alterations of brain stem function, such as lack of eye contact, lack of facial social responses, delays in speech and sensory disturbances (aversion to touch, hypo- or hyper-sensitivity to sounds) while other symptoms like obsessive interests, impairments in expressive language, and heightened memory for details reflect a disruption of higher levels of brain function (Rodier et al., 1996).

1.3.1.3. THE CEREBELLUM

The cerebellum is associated with systems regulating sensory modulation, and motor and behavior initiation. There is evidence of impairment in both of these systems in autism (Dawson and Lewy, 1989; Ornitz, 1989). Recently Schamahmann and Sherman (1998) have detailed cognitive and affective changes in patients with cerebellar disease. Lesions of the posterior lobe of the cerebellum were strongly associated with impairments in executive functions including shifting set, verbal fluency and abstract reasoning, while lesions to the cerebellar vermis were consistently involved where patients demonstrated blunted affect or disinhibited social behavior. Input to the cerebellum along cortico-pontine / ponto-cerebellar pathways and feedback following a cerebello-thalamic / thalamo-cortical route was proposed as circuitry responsible for modulating these higher order behaviors (Schamahmann and Sherman, 1998). It seems that many of the behavioral characteristics seen following cerebellar damage in adults are shared with individuals with autism. However, although the lesions in these patients were confined to the cerebellum, their associated behavioral and cognitive changes are best understood in terms of a more systemic disruption of function resulting from cerebellar disconnection. This view is supported by the observation that there was a recovery of function in most patients and the disruption in behavior was short term. Furthermore, functional imaging (PET/SPECT) in three of the participants indicated hypoperfusion in the parietal, temporal and prefrontal regions indicating a wider loss of function initially (Schamahmann and Sherman, 1998).

Neuropathological findings at autopsy in autism have identified lower Purkinje cell counts, particularly in the more lateral areas of the neocerebellum (Bauman and Kemper, 1985; Bauman, 1991; Rivto et al., 1986). The absence of an accompanying cell loss in the inferior

olive in these cases may signify that cerebellar damage had occurred prenatally, before olivary

climbing fibers had established synapses in the cerebellum (Bauman, 1991).

Courchesne and colleagues reported that on MRI, the medial, phylogenetically older,

regions of the vermis of the cerebellum are reduced in size in individuals with autism

(Courchesne et al., 1988; Courchesne et al., 1994). The vermis plays a role in occulomotor

control (Nagao, 1992) and therefore may contribute to the abnormalities in gaze in autism;

however, a number of researchers have failed to replicate these findings (Filipek, 1995; Garber

and Ritvo, 1992; Hashimoto et al., 1992; Holttum et al., 1992; Kleiman, Neff and Rosman, 1992;

Piven et al., 1992). The identification of corroborative evidence in some, but not all studies

suggests that cerebellar cell loss may not be present in all individuals with autism.

Other factors, such as age and intellectual ability may contribute to the discrepant findings.

In a reanalysis of positive and negative findings Courchesne and colleagues have

identified that in a few cases of autism there is hyperplasia (as opposed to hypoplasia) of the

cerebellar vermis (Courchesne et al., 1994). The idea that areas of the cerebellum in cases of

autism could be over- or under-sized is reasonable from an embryological perspective. Prenatal

injuries to the developing brain can produce rebounds in neurogenesis which may overshoot the

expected cell numbers in the cerebellum (Andreoli et al., 1973). However, while the finding of

both hypoplasia and hyperplasia of the cerebellum helps to explain the disparate MRI

morphological findings somewhat, it also implies that cerebellar abnormalities must play a

minor role in the symptoms of autism. Furthermore, similar reductions in the size of cerebellar

vermis have been reported in juvenile and adult schizophrenia, (Jacobsen et al., 1997;

Nopoulos et al., 1999) suggesting that the changes at the cerebellar level are part of a larger

systemic disturbance of neurodevelopment and not specific to autism.

1.3.1.4. THE LIMBIC SYSTEM

There is evidence of limbic system abnormalities in autism. Autopsy studies have identified reduced neuronal cell size and increased cell-packing density in areas of the limbic system including the amygdala, the hippocampal complex, the subiculum, mamillary body, medial septal nucleus and anterior cingulate gyrus in individuals with autism (Bauman and Kemper, 1985; Bauman, 1991). These structures relate to one another through closely interconnected circuits, that project to areas of the frontal cortex and reticulate brain stem and receive projections from sensory association areas (Bauman, 1991). The observed increase in cell packing density appeared to result from small cell bodies and stunted dendritic arbors, and reflected a large number of abnormally wired cells in these areas (Bauman, 1991; Rapin and Katzman, 1998). A number of other studies have reported abnormal cell formation within the medial temporal lobe structures in autism (including Darby (1976) in 6 of 8 cases with autism, Hof et al. (1991) in one case, and Hoon and Reiss (1992) in one case). On first glance, the evidence of too little brain development in one area of the brain, the cerebellum, and overgrowth of neurons in another, the limbic system, would seem to conflict. These changes may have been produced by developmentally abnormal neurotrophic factors or aberrant programmed cell death (pruning) (Rapin and Katzman, 1998). In the initial stages of normal brain development neurons proliferate and establish many interconnections. Reinforced connections remain, while less favoured connections are pruned, ultimately resulting in greater functional organization of the cortex. It is this process of neuronal growth and pruning that seems to have gone awry in autism, leaving some areas with too few neurons and others with too many.

Evidence of amygdalar abnormalities in autism has been shown in a case study of two

children who demonstrated severe autistic regressions that coincided with the onset of

epileptic seizures (Deonna et al., 1993). Neuroimaging (MRI and CT) identified abnormalities in

the form of calcifications and abnormal tissue densities in the region of the amygdala for both

children. In one child, anti-epileptic therapy led to improvements in cognitive development,

and a reduction of autistic symptoms such that by eight years of age the presentation of the

child no longer met the criteria for a diagnosis of autism (Deonna et al., 1993).

Aylward et al. (1999) recently conducted an MRI study measuring the amygdala and

hippocampus volumes in 14 adolescents and adults with autism and in 14 age, gender and IQ-

matched controls. Measurements were made by two raters, one of whom was blind to group

status. There were no significant differences between the total brain volumes of the group

with autism and the control group. Amygdala volume was significantly smaller for the

participants with autism on measures both with and without correction for total brain volume.

In addition, in measures corrected for total brain volume, the hippocampal size was also

significantly reduced in the participants with autism. The latter finding contrasts with a report

of no significant differences between hippocampal volumes in a group of 35 adolescents and

adults with autism, and controls (Piven et al., 1998). These two groups, though unmatched,

were similar in age and nonverbal IQ. The results were corrected for total brain volume;

however no comparison of total brain volume measures between groups was provided, nor were

comparisons of uncorrected hippocampal measures detailed. It is impossible, therefore, to

assess how large an effect differences in total brain volume might have had on these findings.

It is also difficult to compare these findings with those of Aylward et al. (1999) who controlled

for total brain volume and matched study groups more closely.

1.3.1.5. THE CEREBRAL CORTEX

An MRI study of individuals with autism without an accompanying mental handicap has revealed malformations such as polymicrogyria, macrogyria and schizencephaly in a variety of cortical locations in both hemispheres (Piven et al., 1990). It was suggested that these malformations were the result of a defect in the migration of neurons to the cerebral cortex during the first 6 months of prenatal development.

Abnormal connectivity could be expected to translate into changes in the corpus callosum. The most prominent pathway in the mammalian brain, the corpus callosum is the main transverse fiber tract connecting most, but not all regions of the two cerebral hemispheres. Midsagittal measures conducted on MR images have identified that the thickness of the more posterior portions of the corpus callosum are reduced in autism. These findings have been reported in a study using absolute callosal measures in 51 participants with autism and age matched normal controls (Egaas, Courchesne and Saitoh, 1995) and in a subsequent study of 36 age and non verbal IQ matched participants in which measures were corrected for total brain volume (Piven et al., 1997). Correcting for total brain volume would appear to be an important procedure, in view of the larger total brain volume and head circumferences reported in a number of individuals with autism (Fombonne et al., 1999; Piven et al., 1995). However, increases in total brain volume may not be uniformly distributed across all brain regions, and applying correction factors based on total brain volume may actually diminish or skew findings. For example, Filipek et al. (1992) examined 29 children with autism and found that as compared to normal adult controls, the hemispheric volumes of the parieto-occipital and temporal cortices were greater in the group with autism. In addition, they noted that this increased volume was primarily due to increases in white matter volume. Piven et al. (1995)

reported larger parietal, temporal and occipital lobes measured in 36 teens and young adults with autism, as compared to age and non-verbal IQ matched controls studied by MRI. Typically, it would be expected that an enlargement of the posterior cortical lobes would be reflected in a similar enlargement of the posterior regions of the corpus callosum. As such, the observation of enlarged posterior cortical structures in individuals with autism would seem to run counter to expectation, given the findings of reduced posterior callosal volumes. It has been suggested that this discrepancy may reflect abnormal connectivity between the hemispheres, disruptions of synaptic pruning or alterations in the process of myelination (Piven et al., 1995). It has even been suggested that perhaps it is the frontal regions that are in fact *most* abnormal in autism because they are small relative to the rest of the brain (Piven et al., 1997).

Frontal cortical neuropathology was reported in an early MRI study that identified enlarged anterior horns of the lateral ventricles in a group of 13 children and teens with autism relative to 33 controls selected from clinic cases referred for neurological assessment (Gaffney et al., 1989). These authors suggested that reductions in regions that neighbour the ventricles, like the limbic structures the septum and fornix, could account for the observed differences in size. However, they further noted that it was not possible to measure these small structures given the limitations in slice thickness at the time (Gaffney et al., 1989). Frontal lobe abnormalities have also been reported in a subset of children with autism in an MRI study that focussed on the frontal lobes and cerebellum (Carper and Courchesne, 2000). In this study a group of 42 young children with autism were matched according to age, but not IQ, with community volunteers. The frontal grey matter volumes and the cerebellar vermis were measured in a series of 3 mm contiguous axial images for each participant. A median split of the frontal measures for participants with autism yielded a subgroup with significantly larger frontal grey matter volumes than controls (although these authors did not split the control data

in the same way). It was observed that the frontal lobe hypertrophy in these participants was inversely correlated with hypoplasia of the cerebellum, a relation which contrasted with the more linear pattern observed for these measures in the controls. Unfortunately, these researchers failed to examine the relation between symptom severity, or IQ, and subgroup status even though a battery of diagnostic measures and intelligence testing was carried out.

In a recent study Abell et al. (1999) used voxel-based morphometry to identify regionally specific differences in grey matter volumes in a comparison of high functioning adults with autism and controls (matched for age, gender, handedness and verbal as well as nonverbal ability). Relative to controls, reduced grey matter volumes were identified in the paracingulate sulcus, the left occipito-temporal cortex and the left inferior frontal sulcus of individuals with autism. In addition, increased grey matter volume for the adults with autism was identified in the left amygdala/periamygdaloid cortex, the right inferior temporal gyrus, the left middle temporal gyrus, and in the cerebellum bilaterally. The authors suggested that, with the exception of the cerebellar findings, the abnormal grey matter volumes in the autism group formed part of circuit that centres around the amygdala (Abell et al., 1999). They further theorized that abnormalities in the feed-forward connections that exist between the ventral temporal cortex and the amygdala, and in the reciprocal connections between the amygdala and the inferior prefrontal and anterior cingulate cortices could account of the emotional and social difficulties in autism.

1.3.1.6. SUMMARY OF MORPHOLOGICAL EVIDENCE

The morphometric studies reviewed above have found hypoplasia of parts of the cerebellum, shortening of the brainstem, medial temporal lobe (limbic) abnormalities and reduced posterior corpus callosum in some, but by no means all, cases of autism. The broad, apparently conflicting results are hardly surprising given the variability in the composition of the autistic and control groups, and in the imaging protocols and image analysis methods across studies. There is a great deal of heterogeneity along parameters like age, IQ, gender and symptoms, both within and across the groups imaged in these studies. Variation also exists in the selection of appropriate control groups, with some studies employing neurologically referred medical controls and others using normal control volunteers. Differences in the selection of MRI scanning protocols, anatomical reference points, application of corrections for total brain volume, slice orientation and position also contribute to the variation seen in the reports. The selection of contiguous or non-contiguous slices as well as the slice thickness can also impact on the accuracy of measures. In addition, MR and CT images are subject to volume averaging, where the anatomy observed in a two dimensional slice represents the averaged anatomy through the thickness of that slice. As a result, for example, the anatomy seen in three contiguous 3 mm slices will be more accurate than that observed in a single 9 mm slice. Given these limitations, it is difficult to draw firm conclusions regarding the structural neuroanatomy in autism. However, some of the more recent studies, that have addressed the concerns raised above have produced results that emphasize the role of neuropathology of the amygdala and related limbic structures in autism. The picture will become clearer as work continues to refine and replicate some of the anatomic findings reviewed above.

1.3.2. FUNCTIONAL IMAGING STUDIES

It is apparent, then, that the application of neuroimaging techniques for the purpose of identifying structural abnormalities in autism has yielded widely discordant results. The histological abnormalities that have been observed suggest that the disorder may involve abnormal functional organization, as opposed to focal, region specific damage. For this reason, the investigation of autism using functional imaging techniques offers far greater promise. These methods include Single Photon Emission Computed Tomography (SPECT), Positron Tomography (PET) and functional Magnetic Resonance Imaging (fMRI). In the field of autism, the functional imaging studies conducted to date have either concerned the level or distribution of metabolic activity in the brain or have examined regional changes in brain activity that result from the presentation of a cognitive challenge to groups of participants.

1.3.2.1. FUNCTIONAL STUDIES OF METABOLISM

The first reported PET study of cerebral metabolism in adults with autism was conducted by Rumsey et al., in 1985. They examined the distribution of the regional metabolic rate for glucose in a group of ten high functioning adults with autism and in a group of age matched controls at rest, using [^{18}F]fluorodeoxyglucose (^{18}FDG) and PET. This study failed to identify significant differences between adults with autism and controls in regional cerebral metabolic rate for glucose across 59 regions of interest. In addition, Rumsey et al. (1985) found that although the global mean metabolic rate for the group with autism was about 20% higher than that of controls, the global mean metabolic values for the two groups overlapped considerably. In a subsequent report, Horwitz et al. (1988) added to the data collected in Rumsey's original study (1985), studying an additional four adults with autism. Results similar

to those of the original study were found in the re-analysis; a slight global elevation (12%) in measures of regional cerebral metabolic rate for glucose was noted for the participants with autism over the controls, and only one regional foci out of the 59 ROIs compared distinguished between the groups (a result consistent with chance).

In a subsequent PET study, Herold et al. (1988) failed to identify differences in measures of cerebral glucose and oxygen metabolism in adults with autism and normal volunteers. Six young men with autism (21 to 25 years of age) of average to mildly retarded intellectual ability were compared to an unmatched group of men and women volunteers. A single PET slice through the basal ganglia and temporal grey matter was obtained and regional and global measures of regional cerebral metabolic rate for oxygen, regional cerebral metabolic rate for glucose, and the regional cerebral blood flow were extracted. Herold et al. (1988) reported that there were no significant differences between the adults with autism and the control group, either regionally or globally.

Studies conducted on children with autism have yielded equally varied results. In one, 18 children with autism were studied with PET and [18]FDG (DeVolder et al., 1987). They were compared to 15 adults and 6 children referred for neurological assessment. The make-up of the group with autism was quite heterogenous, with some of the children displaying low to moderate levels of mental retardation. As a result, and to maintain cooperation it was necessary to sedate some of the participants. These authors reported elevated glucose utilization in the children with autism as compared to the adult volunteers. However, the use of sedation and a largely adult control group severely limits any conclusions drawn from this study. It has been reported that glucose utilization rates increase from birth to about 4 years of age, persist at high metabolic rates from age 4 to 10 years, and do not drop to adult levels until 16 to 18 years of age (Chugani, 1998).

In another study of children with autism, ^{133}Xe SPECT was used to determine resting measures of regional cerebral blood flow (Chiron et al., 1995). The control group in this study was selected from neurological referrals for SPECT and assessed retrospectively as normal. Seventeen of the eighteen children with autism were sedated as part of the imaging procedure, while only two of the ten controls received sedation. A pattern of reversed laterality was reported, with the control group having significantly higher left over right hemisphere mean CBF values, and greater right over left CBF values in the children with autism. Unfortunately, any generalization of these findings is tenuous given the study's use of sedation and neurological controls. In another study examining hemispheric laterality, Muller et al. (1998) employed $H_2{}^{15}O$ PET to identify changes in regional cerebral blood flow in 5 adults with autism and controls, during the presentation of tones and sentences. The pattern of activation in controls reflected greater activation on the right for tones and on the left for sentences. This trend was reversed and reduced in the data for the participants with autism prompting the authors to speculate that there may be a reversed hemispheric specialization in autism. However, in this case too, methodological concerns detract from the findings; the participants in this study were not matched on IQ or any measure of language ability, or handedness.

Finally, focal areas of reduced perfusion were reported in the PET scans of 23 children with autism age 2 to 7 years (Ryu et al., 1999). The results of this study, however, are overshadowed by a number of methodological concerns including the lack of a control group, lack of objective measures (abnormalities were determined by visual inspection of the scans) and the use of sedation.

It seems that presently, little can be concluded from the functional metabolic imaging research in autism. No consistent pattern has emerged, and the comparison of studies is

limited by the use of heterogenous study groups, a variety of control groups, and image analysis methods that are open to human error and subjective influence.

1.3.2.2. IMAGING OF COGNITIVE FUNCTION

At this time, the research that has drawn from cognitive neuroscience and applied functional imaging methods to the study of autism has been limited to a few studies on attention, visual figure-ground perception, theory-of-mind and the perception of faces. Buchsbaum et al. (1992) examined the uptake of [18]FDG during the performance of a continuous performance task (sustained attention) in 7 high functioning adults with autism and 13 controls. Glucose metabolic rates were obtained for 42 subcortical regions of interest, and in subdivisions of the cortex in a 2 cm "peel" in three noncontiguous slices. Of the 42 ROIs, the right posterior thalamus and the right putamen showed a significantly lower metabolic rate in participants with autism. These findings are consistent with theories of a brainstem / thalamic pathophysiology in autism (Ornitz, 1989). This study also identified a number of regions with glucose metabolic rates that fell 3 standard deviations or more below the normal mean, and although these outliers were not confined to single location in all 7 participants, there was a trend with greater number of reductions on the right side especially in regions of the frontal lobes. In an expansion of this study, involving 16 participants with autism, Siegel et al. (1992) again found lower glucose metabolic rate in the putamen, and identified a subgroup of adults with autism with abnormally high cingulate cortex metabolism. These findings contradict those of a recent study by Haznedar et al. (1997) in which 7 adults with autism were found to have reduced anterior cingulate volume on MRI and lower anterior cingulate glucose metabolism than controls. These two studies can be distinguished from one another, however, by the demands

each placed on the anterior cingulate region. The question remains as to whether abnormal circuitry results in increased metabolic demand when an area is functionally engaged.

Recently Ring et al. (1999) studied a group of 6 high functioning adults with autism, using fMRI to study the cerebral activation associated with the performance of the Embedded Figures Test (EFT). Previous studies had reported superior performances on this task by individuals with autism (Jolliffe and Baron-Cohen, 1997) and Ring et al. (1999) theorized that the EFT taps certain preserved or superior abilities in autism. Data were collected while participants solved 10 embedded figures designs and during 10 baseline periods where they were simply required to view a blank screen. The results showed that the control participants had more extensive task related activations in the parietal regions bilaterally and the right dorsolateral prefrontal cortex, while the group with autism demonstrated greater relative activation of the right occipital cortex spreading inferiorly to the inferior temporal gyrus. The authors suggested that the results signified that the two groups employed different cognitive strategies in performing the task. The control group tended to use working memory (frontal) and visual search strategies requiring successive shifts in spatial attention (parietal), whereas the participants with autism engaged in greater visual processing extracting information from in-depth feature analysis. It should be noted that the participants with autism in this study were adults, with a mean group age of 26.3 years, and the controls were children, with a mean group age of 5.5 years (standard deviation = 2.8). The rationale behind the selection of such a young control group was not provided. The participants with autism were of average intelligence (mean IQ for the group was 108.5 $\pm$ 10.5) and the EFT was expected to be quite easy for these individuals. As a result, the findings of the study may reflect a less mature processing style for the normal controls as opposed to irregular processing strategies and cerebral activation in autism.

Theory-of-mind was recently studied in a group of 5 adults with Asperger's syndrome and a normal control group using $H_2^{15}O$ PET (Happe et al., 1996). The tasks used in this study required that participants read a passage of text, integrate the content, draw an inference from the context, and attribute mental states to the characters in the stories to solve a question about each passage. The regional cerebral blood flow associated with this task was contrasted, within each of the two groups, with that of a baseline task that involved reading a series of unrelated sentences and answering a question about some detail embedded in the text. The PET data for both normal controls and adults with Asperger's syndrome identified significant areas of activation bilaterally in the temporal poles and in the left superior temporal gyrus. The control group also activated the medial prefrontal cortex, while the participants with Asperger's showed activation of an adjacent but more ventral area of the medial prefrontal cortex. The latter observation lead the authors of this study to conclude that in autism, the neural systems engaged in mentalizing activities are fractionated or lacking some key component (Happe et al., 1996).

A recent fMRI study has also examined theory-of-mind in a group of high functioning adults with autism and a comparison group matched on age, handedness, IQ, socioeconomic status and eduction level (Baron-Cohen et al., 1999). The stimuli used in this theory-of-mind task consisted of photographs of the facial area containing the eyes, accompanied by descriptors of mental state like "sympathetic" and "unsympathetic" or "concerned" and "unconcerned". The same visual stimuli were used in the baseline gender recognition task but were accompanied by the words "male" and "female". The participants selected one of the two words presented, as the best descriptor of the photograph. In controls, the cerebral activation associated with theory-of-mind judgements was identified in the left prefrontal cortex, left medial frontal cortex, middle and superior temporal gyrus, angular and

supramarginal gyrus and the left amygdala and hippocampus. In addition, the control group demonstrated a significantly greater power of response in the left amygdala, left inferior frontal cortex and right insula. The autism group showed activation bilaterally in the superior temporal gyrus and in the frontal regions (though less extensively than the controls), and did not demonstrate any activation in the amygdala. Baron-Cohen and colleagues (1999) suggested that the group with autism had performed the theory-of-mind task without the amygdala, and instead had placed a greater processing load on the temporal regions specialized for verbal labelling.

In an fMRI study by Schultz and colleagues (2000) high functioning young adults with autism and matched controls were required to make same/different judgements during the presentation of pictures of common objects and faces. In the controls, object discrimination resulted in activation of the inferior temporal gyrus, while face discrimination produced activation more medially in the fusiform gyrus. In adult with autism, object discrimination resulted in activation of the inferior temporal gyrus. However, during the face discrimination condition, the adults with autism still activated areas of the inferior temporal gyrus, rather than the fusiform gyrus. These findings lead Shultz et al. (2000) to suggest that their participants with autism had processed the face stimuli as if they were objects, and had relied more on the featural properties of the stimuli rather than on their configural or holistic composition.

Most recently, Critchley and colleagues (2000) used fMRI to study implicit and explicit processing of facial emotion in 9 high functioning adults with autism and in 9 controls. Their participants viewed emotionally expressive faces, and under the explicit condition, were required to judge if each face was happy, angry or neutral. Under the implicit processing

condition, the same stimuli were presented and participants were required to judge whether the faces were male or female. Between group comparisons revealed that with the explicit processing of facial emotion, the adults with autism were distinguished from the controls by significantly greater activation in the left superior temporal gyrus and left lingual/ fusiform regions. The control participants, in contrast, were observed to have significantly greater activity in the right fusiform gyrus relative to the adults with autism. Critchley et al. (2000) interpreted these findings as a failure by the adults with autism to activate the cortical regions associated with the processing of faces when explicitly processing facial emotion. During implicit emotion processing, significant activation was identified in the left cerebellum and left amygdalohippocampal region for the controls but not the adults with autism. Critchley et al. (2000) concluded that their observations of different relative patterns of activity during emotion processing signified a dysfunction, in autism, of the pathways linking the limbic and paralimbic, cerebellar an extrastriate visual regions.

1.4. SUMMARY

The application of functional imaging techniques to the study of autism is an exciting, relatively new opportunity for researchers. It is clear, from the review presented above, that considerable work remains, as future studies attend to the need for replication, homogeneous study groups, adequate controls, and consistencies in imaging methods and statistical analyses. Interpretation of the results from functional imaging studies in individuals with autism and in normal controls suggests that the neuropathology in autism is not localized to one specific area, and likely involves the disruption of a distributed network of functionally related regions.

In particular, the limbic structures including the amygdala, frontal lobes, cingulate gyrus and thalamus have been implicated, as well as the visual association cortices. These findings are consistent with imaging and histological research demonstrating morphological changes in the amygdala and closely related structures.

It has been suggested that the originating neurological insult in autism occurs very early during prenatal development and is observable in changes at the level of the brain stem. The disruption of certain cranial nerves may account for some features of autism, such as abnormalities in postrotary nystagmus or auditory hypo/hyperacusis while other symptoms reflect the disruption of higher centres (Rodier et al., 1996). In the course of development, the cerebral cortex undergoes considerable regional differentiation with the arrival of long noradrenergic, serotonergic, dopaminergic and cholinergic projections from subcortical origins (Berger-Sweeney and Hohmann, 1997). These afferent arrive in the cortex at different times and provide critical signals affecting dendritic length, dendritic arborization, spine density, as well as the morphology and orientation of the developing neurons. In the serotonergic system, the afferent extensions originate in the brainstem raphe nuclei and, therefore, it is suggested that changes in the cortical architecture subserving limbic functions could follow an early insult in the brainstem (though the co-occurrence and precise timing of these changes needs to be studied further).

Earlier in this chapter four socialization deficits in autism were highlighted: reciprocity, joint attention, the perception and understanding of emotion, and theory-of-mind. It has been suggested that children with autism fail to orient to the actions of other people because social stimuli are not marked as rewarding by the amygdala (Waterhouse, Fein and Modahl, 1996). Similarly, amygdala dysfunction in autism may result in a failure to assign

emotional significance to human faces and to the content and intonation of speech. Consequently, speech would fail to be of interest and faces and emotional expressions would not trigger an emotive response in the individual with autism. Finally, a disruption of the frontal regions participating in the regulation of executive functions and emotional behavior may account for both the difficulties understanding / perceiving emotion and the theory-of-mind deficits in autism (Ozonoff, Pennington and Rogers, 1991). Thus there is converging evidence that the socialization deficits in autism result from limbic neuropathology.

CHAPTER TWO

2.1 THE PROCESSING OF FACES AND EMOTION

Efforts to impose some level of organization on the collection of over 20 billion cortical

neurons in the human brain (Pakkenberg and Gundersen, 1997) have lead to the development of

divisions or maps based on architectonic characteristics or functionally localized processing

capacities. Architectonic subdivisions are based on changes in the nature of cortical cell

populations which can be observed as one moves from the highly differentiated 6 cell layers

found in the primary sensory areas to the less distinct 3 or 4 cell layers seen in the allocortical

areas of the limbic system. One of the more common architectonic schemes is the Brodmann's

classification system which divides the cortical surface into 47 zones or areas which are

denoted numerically (eg. Brodmann Area 17, BA 17, see Figure 1). Functional subdivisions

often include comparative cytoarchitectonics in addition to physiological and behavioral indices

of function derived from electrophysiological recordings, functional imaging, and lesion studies.

Five major functional subdivisions of the cortex have been identified; primary sensory-

motor, unimodal association, heteromodal association, paralimbic, and limbic areas (Mesulam,

1998). In general, sensory information is passed sequentially through each of these

subdivisions. Reciprocal connections between one subdivision and the next and parallel

processing streams permit feedback, associative elaboration, attentional modulation and the

initiation of multiple cognitive and behavioral outcomes (Mesulam, 1998).

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The primary sensory areas function as gateways to the cortex as sensory information is processed in these areas first before being passed along to other areas. Primary sensory areas are well delineated both architectonically and functionally and include the primary visual cortex (or the striate cortex, BA 17) found in the occipital lobes, the primary auditory cortex (BA 41-42) which lies on the floor of the Sylvian fissure and the primary somatosensory cortex (BA 3) found along the anterior portion of postcentral gyrus. The primary sensory areas are organized topographically such that each area closely maps the distribution of input in its particular sensory domain.

For example, neurons in the primary visual cortex (BA 17) are mapped retinotopically and are sensitive to movement, orientation, length, spatial frequency, wavelength, luminance and binocular disparity (Shipp et al., 1994).

Figure 1.   Brodmann Areas
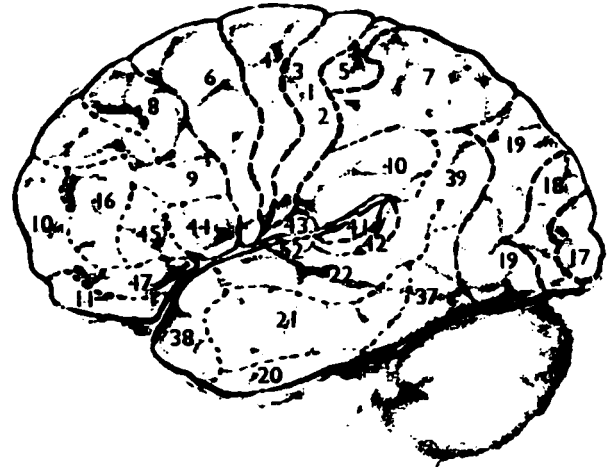
Sagittal plane- lateral surface
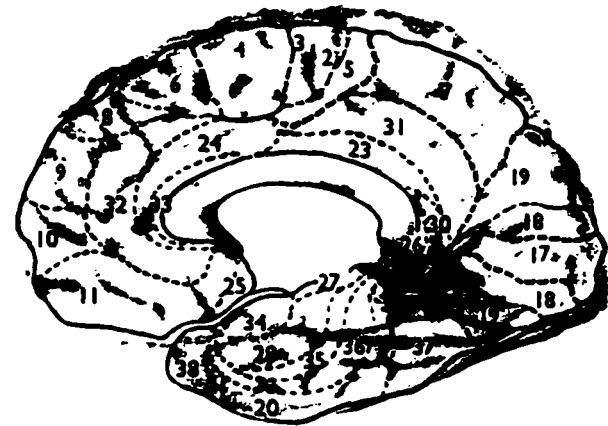
Sagittal plane- medial surface

Information processed by the primary sensory areas is passed next to unimodal association areas. Each of these areas deal exclusively with information from a single sensory modality. In the visual system, the initial encoding of information at the primary sensory level (BA 17) extracts the elementary features of the visual experience. Subsequently, information is passed to the unimodal association areas (BA 18 -19 in the inferior temporal gyrus and the fusiform gyrus) and is directed through parallel interconnections, convergent pathways and feedback loops to yield a compilation of the more composite features of the visual scene.

Neurons in the primary visual sensory area BA 17 project topographically to the unimodal BA 18 and both BA 17 and BA 18 give rise to a number of multiple parallel pathways that extend first to BA 19 (Felleman and VanEssen, 1991) and then predominantly along two divergent pathways, one directed dorsally toward the parietal cortex and another projecting ventrally to the visual association areas of the inferior temporal lobes (Ungerlieder and Mishkin, 1982). The dorsal visual stream is specialized for spatial location and the detection of motion, whereas the ventral stream is involved in the discrimination of colour, form and pattern (Allison et al., 1994). Still further downstream ventrally, there are cell assemblies specialized for object and face identification (BA 20, BA 18 and BA 37) located in the mid portion of the fusiform gyrus (Tranel, Damasio and Damasio, 1995; Kanwisher, McDermott and Chun, 1997).

The suggestion that there is a face specific subsystem in the ventral pathway is consistent with the evolutionary and social importance attached to the processing of faces. It is also consistent with observations of propospagnosia or an inability to recognize faces, seen with lesions in this area. In fact, lesions can result in quite selective deficits in the processing of categories indicating a considerable functional segregation in the ventral stream (Moore and Price, 1999). While the number of subsystems or categories is still under debate, most models

distinguish face processing from other categories (Farah, 1990; Allison et al., 1994).

Evidence of a face specific region in the fusiform gyrus is found in a study that examined the recordings from cortical surface electrodes implanted in epilepsy surgery patients. The visual presentation of faces or letter strings to these patients excited neurons in regions of the fusiform and inferior temporal gyrus that fired selectively in response to the face stimuli but not to the letter strings (Allison et al., 1994). In similar patients, direct electrical stimulation of the right occipito-temporal cortices can disrupt the processing of facial information (Fried et al., 1982). Similarly, magnetoencephalographic (MEG) recordings have revealed occipito-temporal responses specific to faces in four of seven participants (Sams et al., 1997).

Inferior occipito-temporal activation has also been demonstrated in a variety of regional cerebral blood flow studies with face processing tasks, including the categorization of famous faces versus familiar objects (Sergent, Ohta and Macdonald, 1992), the recognition of familiar faces (Andreasen et al., 1996), the matching of facial identity as compared to spatial location (Haxby et al., 1994) and the initial encoding of faces for subsequent recall (Haxby et al., 1996).

Finally, additional evidence of face specific modules in the extrastriate visual cortex is found in fMRI activation studies demonstrating significantly greater fusiform activation during the passive viewing of faces, as compared to scrambled nonsense patterns (Puce et al., 1995), letter strings (Allison et al., 1994) or familiar objects (Kanwisher, Chun and McDermott, 1996).

In some studies the volumes of activation have been larger in the right hemisphere than in the left (Haxby et al., 1994 ; Puce et al., 1995). In addition, unilateral activations in individual participants have been observed more frequently in the right hemisphere (Kanwisher, McDermott and Chun, 1997), and it has been suggested that there is a right hemispheric dominance in visuoperceptual face processing (Sams et al., 1997). Analysis of single subject data in fMRI studies has identified a high degree of intrasubject test-retest consistency,

strengthening the argument for faces specific modularity (Puce et al., 1995; Kanwisher,

McDermott and Chun, 1997). However, across participants, there is considerable variability in

the extent and location of activations, with the majority demonstrating either unilateral or

bilateral activation of the fusiform gyrus, and a minority failing to show any activation in this

area at all (see Puce et al., 1995). Two plausible explanations have been offered for these

observations. The first is that current imaging methods are not sensitive enough when

individual participant data are considered. The second proposes that processing may be more

or less distributed across the two cerebral hemispheres, and that it should be considered within

a developmental context. It has been observed that newborn infants display a preference for

face stimuli over non-face stimuli of equal complexity, and that over the first 6 months, infants

show marked improvements in their capacity to discriminate faces (Ellis, 1992). In infancy,

subgroups of neuron cell populations may be tuned for the encoding of objects and faces.

Individual experience would act upon these neurons and dictate the distribution or

lateralization present in the final cortical organization (Allison et al., 1994). Similar

experiential modification of neuronal groups has been suggested to account for the location of

visual word forms in the ventral stream object areas, which have been acquired quite recently

in phylogenetic terms (Mesulam, 1998). It is important to note, therefore, that the

specialization of unimodal association areas for the identification of colour, movement, objects

or faces is not absolute. Processes localized to particular regions may be distributed more

broadly and neighbouring areas may participate in the processing attributed to a particular

locale, although to a lesser degree (Mesulam, 1998).

The specialization of the unimodal association areas extend beyond visual perception to

a role in memory and learning. Fahy et al. (1993) have found that in the monkey, neurons in

the anterior inferior temporal areas demonstrate a familiarity response as long as 24 hours

after an initial exposure to faces. Patients with bilateral lesions of the inferior occipito-temporal region demonstrate an inability to recognize previously familiar faces including their own face, yet remain capable of naming object classes, such as a specific car as a car (Damasio, 1985). Such observations have led to the suggestion that temporal lobe association cortices have a storage function for object vision (Mishkin, Ungerlieder and Macko, 1983). It has been further suggested that the retrieval of conceptual knowledge relies on the activation of these early association areas which aid in the reconstruction of explicit images or exemplars of a concept (Tranel, Damasio and Damasio, 1997). Observation of fusiform and lingual gyri activation in a PET study involving the recognition of familiar faces is consistent with this notion (Andreasen et al., 1996).

The remainder of the functional divisions of the cortex are the heteromodal, paralimbic and limbic divisions. These areas are reciprocally connected to more than one unimodal area and thus identified as multimodal or transmodal. They support the convergence of multimodal information and are thought to link distributed unimodal processes through the creation of directories or look-up tables (Mesulam, 1998). Thus, it is suggested that modality specific information is bound into multimodal representations that are spatially distributed within the neural tissue and result in convergent processes. Processing is conceptualized in terms of a functional network, or architecture, in which activations are distributed both physically and temporally (Friston, 1998). Multimodal association areas in the dorsal processing stream have been associated with the activation of the dorsal parietal cortex during spatial memory processes and imagery (Roland and Friberg, 1985; Owen et al., 1996). The existence of multimodal convergence zones in the ventral stream has been elegantly detailed in a study by Buchel et al. (1998). In this study it was observed that when congenitally blind, late blind or sighted participants were presented (Braille or visually - according to group) with words and

non-word letter strings, common areas of the basal temporal lobe were activated, thus

demonstrating the convergence of visual / tactile information with phonological and semantic

knowledge.

Recently, studies have distinguished between posterior temporal activation attributed

to the processing of object features, from more anterior temporal activations involved in

accessing semantic knowledge (Moore and Price, 1999). With regard to face processing, lesions

to transmodal areas in the anterior temporal poles have been shown to impair the capacity to

recognize famous faces (Tranel et al., 1997). Similarly, the process of recognizing familiar

faces is distinguished from visuoperception of unfamiliar faces by the activation of transmodal

areas of the midtemporal cortex, (over and above the activation of unimodal fusiform areas).

These transmodal areas appear to be important in the recognition of a familiar faces, linking

the visuoperceptive features of the stimulus to an associative network that binds the name,

the voice, expressions and past recollections specific to that face (Tranel et al., 1997).

Finally, activation of transmodal areas of the right inferior frontal cortex has

accompanied inferior occipito-temporal activation in PET regional cerebral blood flow studies

involving identity recognition (Ungerleider, Courtney and Haxby, 1998; Haxby et al.,1994).

In one study, it was suggested, that the activation of the inferior frontal cortex reflected the

demands placed on working memory by the task (Haxby et al., 1994). The inferior frontal

cortex is a projection zone of neurons in the ventral stream (Chavis and Pandya, 1976; Webster

et al., 1994) and receives convergent multimodal input important in response selection (Kapur

et al., 1996; Haxby et al., 1997). Petrides et al. (1993) have shown that adjacent yet

functionally separate areas of the mid-inferior frontal region are involved in aspects of working

memory and response monitoring and selection (BA 9, BA 46 and BA 8, respectively).

Unilateral activation of right inferior and mid-prefrontal areas (BA 45/47 and BA 46/9) has been

identified in a study examining face working memory (Ungerlieder, Courtney and Haxby, 1998).

In addition, right hemispheric laterality for face memory has been reported in another study

that contrasted memory for faces with spatial working memory (Smith et al., 1998). However,

Ungerlieder, Courtney and Haxby, (1998) have reported bilateral activations under similar

experimental conditions, and demonstrated left lateralization of working memory under

conditions that encouraged symbolic or verbal encoding of the faces and right lateralization

under conditions that permitted more image-based encoding. Laterality effects, they

suggested, were a function of task demands which affect the extent to which participants

engage in symbolic or verbal encoding (Ungerlieder, Courtney and Haxby, 1998).

The last functional division is the limbic system, and, although included above within

the context of transmodal processes, this system plays a particularly important role in linking

the internal environment to external events. The wide distribution and richness of cortical-

limbic interconnections has led to the suggestion that the limbic system exerts a tonic influence

over the cortex (Barbas, 1995). In particular, the amygdala, through its bidirectional

connections with umimodal association cortices in the superior and inferior temporal gyri

(Aggleton, 1993) may play an important role in modulating sensory responses according to their

acquired intrinsic or emotional significance. In this way, the amygdala, is thought to bind the

emotional and motivational valence of experiences to their sensory representations.

Lesions of the amygdala can result in deficits in the recognition of facial emotions,

especially for expressions of fear (see Anderson and Phelps, 1998). Bilateral lesions of the

amygdala can specifically disrupt the recognition of facial emotion (Adolphs et al., 1994).

Procaine induced anxiety, or euphoria, in participants has been associated with bilateral

activation of amygdalo-parahipocampal and insular cortices (Servan-Schrieber and Perlstein, 1997). Increases in amygdala and temporal lobe activity have been reported in a cerebral blood flow study that required participants to mimic the emotions portrayed in photographs ("experimentally induced emotions") (Grodd et al., 1995). Regional cerebral blood flow data has also distinguished between activations associated with viewing happy and fearful emotions, identifying left amygdala activation for participants when they viewed fearful expressions, and activation of the right medial temporal gyrus with happy expressions (Morris et al., 1996). In addition, it was observed that measures of regional cerebral blood flow increased monotonically with increases in the intensity of the emotion portrayed in the fearful facial expressions (Morris et al., 1996). Expressions of fear and disgust were contrasted in a related study employing fMRI (Phillips et al., 1997). Again the presentation of fearful faces resulted in amygdala activation, while faces depicting disgust were associated with activation of the right insula, an area associated with pleasant and unpleasant gustatory responses (Phillips et al., 1997). Most recently, changes in regional cerebral blood flow have been measured in participants asked to make gender discriminations while viewing stimuli that depicted sad and angry facial expressions (Blair et al., 1999). Sad expressions were associated with increased activity in the left amygdala, while angry faces generated orbito-frontal and anterior cingulate activity.

The frontal lobes also participate in the modulation of neural responses to sensory experiences that have become emotionally significant. The anatomic connectivity of the amygdala with the inferior lateral and orbital frontal areas suggest a prominent role for these structures in the modulation of emotional experiences. Lesions in the orbito-frontal cortex lead to social isolation, decreased affiliative behaviour, impaired social communication, shallow affect and a lack of appreciation for social rules (Damasio and VanHoesen, 1983; Deutsch et al.,

1979; Franzen and Meyers, 1973) and impairments in emotion recognition (Hornak, Rolls and Wade, 1996). Kolb and Taylor (1988) have found that relative to lesions in other areas of the brain, both left and right frontal lesions result in significant impairments in the ability to match facial expressions of emotion. Other lesion studies have also highlighted the importance of the inferior frontal cortex in affect recognition (Hornak, Rolls and Wade, 1996).

A recent PET study that asked women to recall emotionally laden personal experiences while viewing pictures of corresponding facial affect found bilateral activation of inferior frontal and orbitofrontal regions for sad emotions and deactivation of the right prefrontal and temporal-parietal regions for happy emotions (George et al., 1995). In another PET study, increases in regional cerebral blood flow during an emotion discrimination task were observed in left frontal regions during happy discriminations whereas right parietal activations were observed during sad discriminations (Gur et al., 1994). George et al. (1993) have used $H_2^{15}O$ PET to identify the areas of cerebral activation associated with matching happy and sad facial emotions. They found that the right anterior cingulate gyrus and the bilateral inferior frontal cortex (BA 45) were activated in normal female adults during the performance of an emotion matching task. In this study the activation for emotion trials was contrasted with that observed for an identity recognition task. A contrast of the identity recognition task with a baseline task requiring spatial location matching revealed significant activation of the visual cortex (BA 17 and BA 18; George et al., 1993). Inferior frontal activation with the processing of facial emotion has been reported in a number of other functional imaging studies (Nakamura et al., 1999; Narumoto et al., 2000). Other imaging studies have demonstrated activation of the inferior frontal region with the processing of emotion in voices (Kawashima et al., 1993; Zatorre et al., 1992). Collectively, these finding demonstrate that the processing of facial identity involves, at a rudimentary level, the unimodal cortices, while emotional processing engages

additional multimodal frontal regions.

The process of discerning emotion in the faces of others would seem to engage a number of functional divisions of the cortex; involving the occipital lobes in the analysis of the visual input, engaging the association areas in the ventral stream in the processing of facial information, calling on multimodal temporal regions to integrate memory and information available from other sensory modalities, drawing on the amygdala to acquire an emotional valence, and engaging the frontal lobes to draw the whole experience together use it to guide subsequent action.

The notion that emotion recognition involves a number of functionally related yet regionally distributed areas is demonstrated in a recent study by Streit and associates (Streit et al., 1999). MEG recordings were taken while adults categorized familiar objects during one trial and facial emotions during the next. The good temporal resolution of MEG allowed these researchers to identify the areas involved in facial emotion recognition sequentially, with the earliest activations in emotion recognition appearing in the superior right temporal cortex and inferior occipitotemporal cortex. This was followed by activation in the middle area of the temporal cortex . The authors considered these results to be consistent with face processing (fusiform) and involvement of neurons within the ventral stream. The next region to become active was the amygdala, underscoring its importance in evaluating the emotional significance of incoming sensory information. The last two regions activated with emotion recognition were the right anterior cingulate followed by the left inferior frontal cortex. The cingulate forms part of the limbic system, bridging amygdala and the frontal cortices. Streit et al. (1999) suggested that the process of drawing elaborate associations to judge emotion in faces may draw on frontal working memory functions. This suggestion is consonant with the view that the

prefrontal cortex mediates working memory representations that help to guide processing in the absence of external perceptual cues (Goldman-Rakic, 1988). However, George et al. (1993) also reported activation in the inferior frontal region with emotional stimuli, and suggested that task demands of their emotion matching task and its comparison task, an identity matching task, were relatively similar (as indicated by the response patterns of their participants). They concluded that the working memory demands were relatively similar across the two tasks and that the inferior frontal activation was associated with the processing of emotion. Therefore, It may be suggested that this inferior frontal activation reflects either a frontal response selection mechanism (Petrides et al., 1993) or the joint participation of limbic and frontal areas in the emotional experience.

These findings indicate that the recognition of facial expressions of emotion is a process that relies upon activity in several brain regions (Streit et al., 1999). It has been suggested that facial affect recognition is mediated through a multiplex circuitry that is relatively independent of the neural systems responsible for extracting other non-affect related features of faces (Dimberg, 1990). In fact, the observation of emotion specific activations has lead to the conceptualization of dissociable yet interlocking system that involves an interplay between temporal, amygdalar, cingulate and frontal cortices (Blair et al., 1999).

2.1.1. SEX DIFFERENCES IN THE PROCESSING OF EMOTION

The research identifying sex differences in cognitive function is extensive. Females tend to excel verbally, being more articulate and fluent than males. On the other hand males tend to perform better on tasks that involve spatial relations (Kimura and Harshman, 1984).

It has been well established that in right handed individuals, the left hemisphere is primarily concerned with the processing of verbal functions while the right hemisphere is involved with spatial processing (Milner, 1971). The distribution of these processes in males is more highly lateralized than in females, in whom processing appears to be spread across the two hemispheres (McGlone, 1978; Shaywitz et al., 1995; Davatzikos and Resnick, 1998). Studies of the effects of unilateral cerebral lesions have shown that females are less likely to demonstrate as severe deficits in spatial processing with damage to the right hemisphere, as compared to males with lesions confined to the right side (McGlone, 1977; Inglis et al., 1982). Similarly, with damage to the left hemisphere, verbal processing abilities tend to be less affected in females than in males. Presumably the greater lateralization of cognitive function in males increases the negative consequences of unilateral lesions. Physiological evidence of sex differences in lateralization has been identified by Butler (1984), who found greater hemispheric lateralization in the EEGs of right handed males with right handed immediate relatives during the performance of mental arithmetic and face recognition tasks than in similarly matched females. Tachistoscopic studies involving the presentation of verbal or spatial tasks to the left or right visual hemifield, have also identified less lateralization of cortical function in females (Kimura and Harshman, 1984).

In addition to spatial processing, the right hemisphere plays an important role in emotional experience (Gainotti, 1972). Many reports have identified impaired processing of emotional faces, or scenes, subsequent to right hemispheric damage (Borod, 1992; Bowers et al., 1985; Adolphs et al., 1996). Furthermore, studies of individuals with right hemispheric lesions have found reduced physiological changes to emotional stimuli on the galvanic skin response, a measure of autonomic nervous system function (Morrow et al., 1981; Schrandt et al., 1989).

While these studies underscore the importance of the right hemisphere in emotion processing, Mandal, et al. (1998) have cautioned that the localization of function from lesions studies is problematic because of the co-location of spatial and emotion processes on the right. In fact, elements of the emotional experience appear to be available to both hemispheres. Gazzaniga and LeDoux (1978) presented split brain patients with visual stimuli and asked them to both describe each item as well as provide a rating as to how much they liked or disliked each of the stimuli. Only stimuli presented to the right visual field (and therefore being processed by the left, verbal, hemisphere) were described accurately. In contrast, the affinity that participants held for the items presented to each visual field was identical, indicating equal hemispheric access to subjective emotional experiences (Gazzaniga and LeDoux, 1978).

To complicate matters further, some researchers have proposed that the hemispheres are specialized according to the valence of the emotion (Levental and Tomarken, 1986). There are two main hypotheses regarding hemispheric specialization for emotion in the neuropsychological literature. The first holds that the right hemisphere is specialized for emotion regardless of valence, while the second maintains that the right hemisphere is specialized for negative emotions, and the left for positive emotions (Heller, 1993). However, some further distinctions are drawn in the latter hypothesis, such that hemispheric specialization for emotion perception, regardless of valence, is considered a right hemispheric function, while emotion expression shows the negative-right / positive-left split.

Sex differences in the processing of emotion have been identified in a number of studies. Not only do men perform emotion discrimination tasks more poorly than women, but in particular, they seem less sensitive to female expressions of sadness (Erwin et al., 1992). Women, in contrast, are more receptive to emotion viewed in male faces than female faces

(Erwin et al., 1992). This greater receptivity toward male faces by women is intriguing because researchers have found that under similar experimental conditions the facial expressions of women are more emotionally expressive than those of men (Allen and Haccoun, 1976; Wagner et al., 1993).

Physiological evidence of sex differences in emotion processing has been identified in a recent study by Kring and Gordon, (1998). These researchers found that the galvanic skin responses of men and women who viewed emotionally laden films differed, with men demonstrating greater reactivity to fear and anger films, as compared to women who reacted most to films depicting sadness or disgust. Differences between men and women have been identified in measures of regional cerebral blood flow during the recall of personal experiences to "self induce" sadness or happiness (George et al., 1996). Despite similar self-reported mood changes for males and females, the women in this study activated a significantly wider portion of their limbic system during the transient self induced periods of sadness (George et al., 1996). The participants in this study were also presented with images of emotionally expressive faces while they attempted to self induce an emotional state, and therefore, these results appear to relate to both the processing facial emotion and self imposed changes in mood state. Other functional imaging studies of facial emotion processing have studied either all female (Lane et al., 1998; George et al.,1993), all male (Blair et al., 1999) or mixed study populations (Phillips et al., 1997; Morris et al., 1996) and have not directly addressed the question of sex differences in emotion recognition.

In one PET study of emotion recognition bilateral increases in regional cerebral blood flow in the inferior frontal cortex was reported for a group of female participants (George et al., 1993). It is of interest, here, that the activation identified in this study involved both

cerebral hemispheres. While this finding seems to contradict the view that emotional processing is primarily a function of the right hemisphere, it is in keeping with the idea that the differentiation of cerebral function in females is less lateralized. The recent study by Nakamura et al. (1999) examined facial emotion processing in a group of male participants, and identified activation solely of the right inferior frontal cortex. These findings are consistent with the suggestion that there is a greater lateralization of function in males. Imaging studies of facial emotion processing that have examined groups comprised of both males and females have reported findings for the full group, and not distinguished between the activations for male and female participants. It remains to be seen, under similar experimental circumstances, whether the cerebral activation during emotion recognition for males would differ from that observed for females. We might expect however, that with facial emotion processing, females would engage a broader distributed network of functional areas than males, and that this would include bilateral activation of the inferior frontal cortices.

CHAPTER THREE

3.1 POSITRON TOMOGRAPHY

In this chapter a brief description of Positron Tomography (PET) will be presented, as well as the common methodological elements used throughout the thesis.

Recent advances in technology have made it possible for scientists to study the connections between cognition and neuroscience, between mind and brain. It is now possible to render certain aspects of thought visible by recording its physical effect on brain activity using PET (for example, George et al., 1993; Blair et al., 1999). PET is an imaging technique that provides images of the spatial and temporal distribution of radioisotopes introduced into the body for the purpose of studying biological, physiological and metabolic processes in vivo.

The exploration of human brain function with PET has been made possible by the observation that neuronal activity is closely coupled to changes in regional cerebral blood flow (rCBF) (Baron et al., 1982). The preferred methods of measuring rCBF using radioisotopes, involve the inhalation of $C^{15}O_2$ (Lammertsma et al., 1990) or the injection of $H_2^{15}O$ (Herscovitch et al., 1983; Raichle et al., 1983). The short half-life of ^{15}O *(123 seconds)* permits repeated measures of regional cerebral blood flow to be collected in a single participant within one scanning session lasting approximately one hour. The capacity to perform multiple acquisitions within one sitting provides an opportunity to introduce changes in the conditions under which regional cerebral blood flow measurements are collected. The combination of carefully designed changes in cognitive processing demands with the relatively high spatial resolution

imaging of PET (voxels of about 5 mm to a side), provides a powerful tool for studying the

neurological origins of cognitive processes. This chapter provides an outline of the

fundamentals of the ^{15}O PET study, reviewing the intricacies of acquiring PET images, the

details of an ^{15}O protocol, and the image processing steps required before statistical inferences

can be drawn from rCBF data.

3.1.2. THE ATOM

Atoms with nuclei that are proton-rich become stable through either positron emission

or electron capture. The latter occurs more often in atoms with heavy nuclei in which the

strong positive nuclear charge draws orbital electrons inward. The former, positron emission, is

the predominant process for lighter elements, including atoms that are important in biological

systems like Carbon, Oxygen and Nitrogen. However, this mode of decay can only take place if

the parent atom is heavier than the daughter atom by at least 2 electronic masses (equivalent

to 2 x 511 kev).
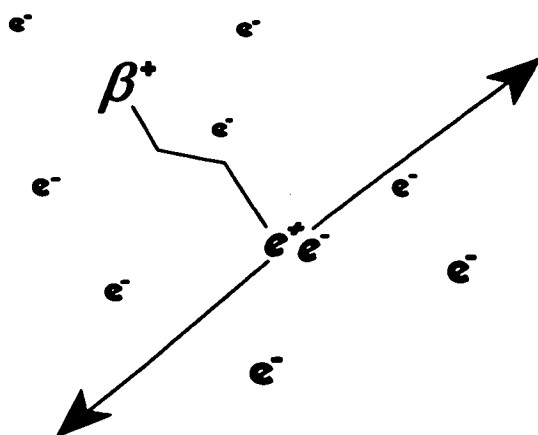
Figure 2. Positron Annihilation

β^+	positron emitter
e⁺	positron
e⁻	electron
⟶	511 kev gamma ray photon

The positron, upon emission from the nucleus travels a very short distance, (1 to 6 mm)

losing energy through interactions in surrounding matter and slowing until its kinetic energy

reaches thermal levels. It then interacts with a local neighbouring electron and through mutual

annihilation, two 511 keV photons are produced. The photons travel away from the point of

annihilation at close to 180° to each other. The detection of both photons in coincidence

makes it possible to define a line along which the annihilation has taken place and provides the

foundation of PET imaging.

3.1.3. THE TOMOGRAPH

In contemporary positron tomographs,
photons are detected using scintillation crystals
of bismuth germanate ($Bi_4Ge_3O_{12}$;BGO)
coupled to photomultiplier tubes (Figure 2).
These scintillation detectors are arranged in a
series of rings around a patient porthole.

The tomograph used in the present
study is the Siemens/CTI ECAT 953 /31 at
McMaster University. A single BGO crystal is
divided into an 8 X 8 grid of detector cells by
fine cuts extending inward from the face of
the crystal and is mounted onto four
photomultiplier tubes. When a photon hits
the detector, the location of its interaction

Figure 3.   BGO crystal and
              Photomultiplier Unit

photomultiplier tubes

BGO crystal
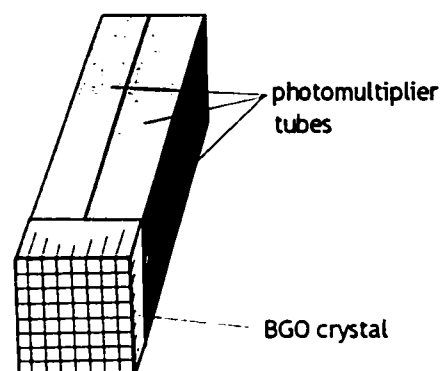
Figure 4.   One Bucket
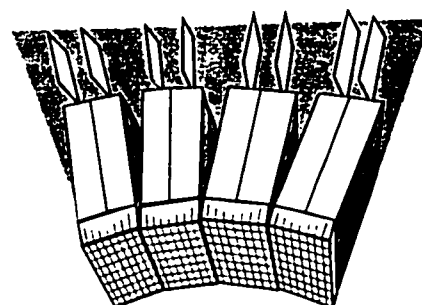
within the 8X8 grid is identified by combining the relative scintillatation light collected from the four photomultiplier tubes using Anger-type logic.

Four adjacent crystals and their associated photomultiplier tubes share a common electronics unit and make up a bucket (Figure 4). Twelve buckets are arranged in each ring around the 35 cm patient port and there are 2 rings of buckets in total, with an axial coverage of 10.8 cm (Figure 5). Interplane septa of tungsten may be extended to collimate the detector rings or retracted as in the protocol used in this study.

Figure 5.   The Positron Tomograph

3.1.4. DATA ACQUISITION

To conduct a PET study a chemical labelled with a positron emitting isotope is introduced into the participant through inhalation or injection and the participant is positioned such that the organs of interest are within the field of view (FOV) of the tomograph (Figure 6). As the isotope decays, the resulting annihilation photon pairs travel through tissue and air.

Figure 6.   Location of Participant
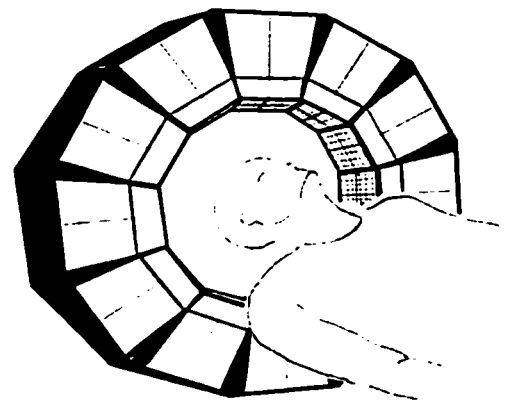
Photons arriving at two opposing crystals, at the same instant in time, define a line along which the positron annihilation has taken place (Figure 7). This is the Line of Response (LOR).

The location in space of the LOR connecting two detectors is defined by the angle it makes with a reference direction (θ in the xy plane) and its radial distance (r) from the center of the FOV (Figure 8). Starting with a single point in the field of view, a LOR passing through that point, connects two opposing detectors. Relative to this LOR, a number of parallel LORs (connecting other detector pairs on the ring) with the same angle but different radial distances can be identified. Rotating to the next detector pair defining a LOR through this point, identifies a further set of parallel LORs at this new projection angle (Figure 9). Proceeding, in this fashion in plane around a single ring in the ECAT 953/31 produces data for 160 parallel LORs at each of 192 projection angles. These data from a fixed scan interval, or frame, are stored in a matrix called a sinogram.

Figure 7.   Line of Response
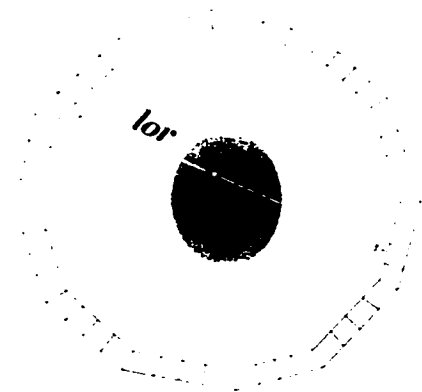
Figure 8.   Defining the LOR
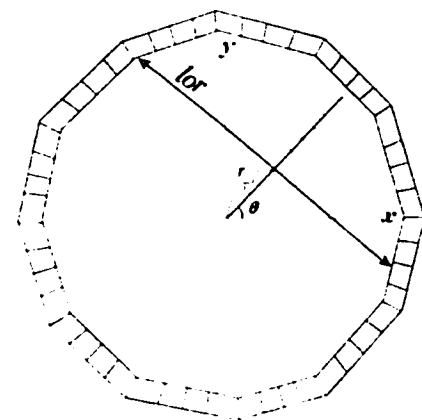
Figure 9.   Parallel LORs
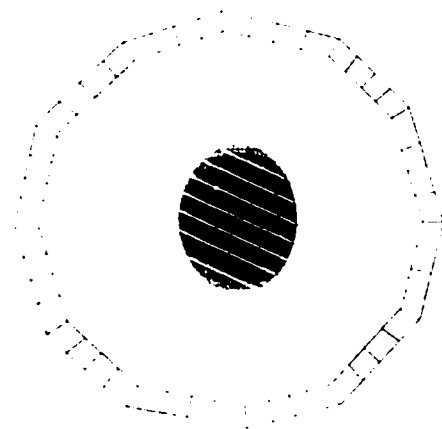
The sinogram derives its name from the fact that any point source will describe a sinusoidal path in such a matrix. Sinograms are formed for each of the 16 rings of detectors (direct planes). It is also possible to collect coincidence counts between detectors located in immediately adjacent rings. This results in data stored in 15 additional cross plane sinograms for a total of 31 sinograms.

3.1.5. NORMALIZATION

The sensitivity of each detector will differ, and therefore a method is required to correct for the relative efficiencies of each detector pair. A scan of a rotating plane source or of a centrally located phantom source can be used to measure the sensitivity of each detector pair. From this information normalization factors can be calculated and applied to scale the LORs in data collected in the scan of a participant.

3.1.6. SCATTER

Scatter occurs when one (or both) of the emitted photons are deflected en route to the detectors through the process of Compton scattering. If a photon pair is detected when one or both photons have been scattered, the LOR identified by the tomograph will not pass through the point of annihilation (Figure 10).

Figure 10.   Scatter
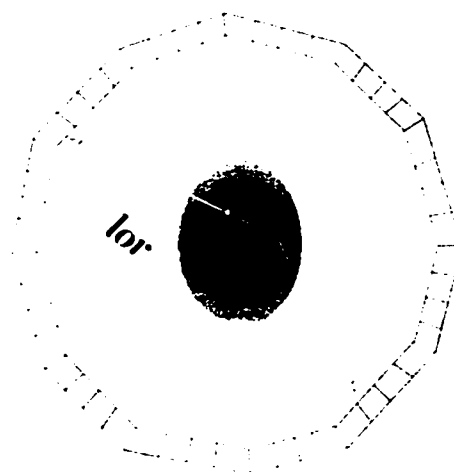
Recording these events adds noise and incorrect data to the sinogram and results in a loss of image contrast and quantitative inaccuracies in the distribution of isotope. However, in general, scattered photons are of lower energy than unscattered ones, and therefore fewer incorrect LORs will be identified if only photons with energies that fall within a preset energy window (eg. above 350 keV) are recorded. Unfortunately, there will still be some scattered photons with energies high enough to be included in this energy window. To correct for these events, a second set of LOR readings is recorded at a lower energy window and a fraction of the sinogram data from this window is subtracted from the sinogram data recorded at the upper energy window to remove some of the scatter in this data.

3.1.7. ATTENUATION

As annihilation photons travel through tissues many will undergo Compton scattering and/or photoelectric absorption. The resulting loss of coincidence events is called attenuation. Most of the interactions for 511 keV photons travelling through soft tissues are Compton scatter events (as described above), and a few photoelectric interactions are expected predominantly in bone. Generally, the further a photon has to travel through tissue and air on the way to a detector, the greater the chance it will be attenuated.

Ninety percent of photons are deflected when travelling through 20 cm of tissue equivalent (Personal communication, Asselin, 2000). One method of correcting for attenuation, in studies of the brain, involves reconstructing the images, and then positioning an ellipse around the cranial volume in each image slice in the axial plane. An attenuation correction factor can then be calculated using the chord length of the LOR through the outlined ellipse and a linear attenuation coefficient appropriate for the tissue under consideration

(0.095 cm^{-1} for brain at 511 kev). These correction factors can then be applied to the original emission projection data and submitted for reconstruction to yield attenuation corrected images. A second approach for correcting for attenuation involves the use of an external positron emitting source and two transmission scans; one performed with no object in the field of view of the scanner (blank) and the second one done while the participant is positioned in the scanner (transmission). The attenuation correction factor can be calculated as a ratio of the blank/transmission data, and applied during image reconstruction.

3.1.8. MULTIPLE AND RANDOM COINCIDENCES

A multiple coincidence event occurs when more than two photons are detected simultaneously (ie. within the timing window of the tomograph). Unfortunately, in this instance a LOR cannot be defined and these events must be discarded. Random coincidences occur when two annihilations occur almost simultaneously and one photon from each of the annihilations is registered at a detector. In this instance, a coincidence event will be recorded falsely for the LOR joining the two detectors. The rate at which random coincidences occur can be estimated from the number of single events recorded by each detector pair.

Figure 11.   Random Coincidences
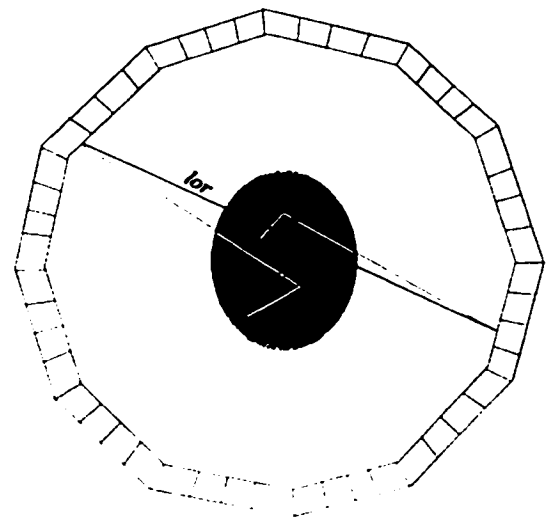
3.1.9. RECONSTRUCTION

Presently, the method used to reconstruct images from the ECAT 953 /31 is filtered

back projection. The activity in each volume element or 'voxel' is estimated by projecting

the emission data back across the image space. Where data interfere, there is an increase in

the density of the voxel. The projection data is filtered to account for the change in

coordinate systems that describe the image space and the projection space.

3.1.9.1. RECONSTRUCTED IMAGES

Figure 12.   Patient Location

The Cartesian co-ordinate system applied to

reconstructed PET images is fixed relative to the

tomograph (Figure 12). Facing the patient port of the

tomograph; the X-axis runs horizontally from

left to right; the Y-axis runs vertically from the

bottom of the port to the top and the Z axis runs

horizontally from the front of the patient port to the

back. With reference to images of a participant lying

supine, positioned headfirst in the scanner, the X plane runs in the sagittal direction left to

right, the Y plane runs coronally and the Z plane divides the image into transaxial slices.
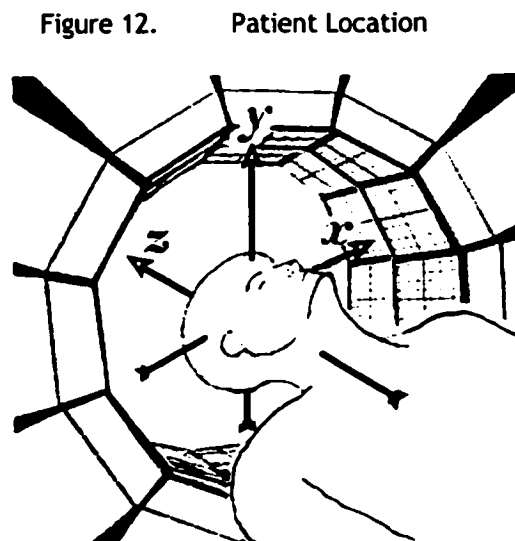
The scans in the present research were performed with the ECAT 953 /31 tomograph.

The scans were corrected for attenuation and scatter, and were reconstructed using filtered

back projection with a Hanning filter and a cut off frequency of 0.30 cycles per voxel.

Each voxel measures 1.96 x 1.96 x 3.38 mm^3 (X x Y x Z) and the image dimensions are

128 x 128 x 31 voxels in the x,y and z planes respectively. Figure 13 presents transaxial

sections of an image reconstructed from a scan conducted on the author utilizing ^{15}O in the protocol described in section 3.3.

3.1.10. RESOLUTION

The accuracy with which PET is able to quantify the distribution of an isotope, and resolve the activity identified in one structure from another is affected by the spatial resolution of the scanner. Limitations on the resolution of images are imposed by the distance travelled by the emitted positron prior to annihilation, the slight non-collinearity of photons, the size of the BGO detectors and a ceiling on the number of available counts which results from limits in acceptable patient dose exposure (Phelps et al 1986). While scanners may be built with finer and finer detector sizes, there is a point at which reductions in detector size will not improve the resolution of the scanner. This is because of a relation between detector size and detector efficiency; as detector size goes down, so do the counting statistics for each LOR. Thus there is a trade off between detector size and counting statistics that limits the resolution that is achievable in PET. The resolution of the PET scanner is a measure of the smallest distance over which two photon emitting point sources can be distinguished and is expressed as the full width half maximum (FWHM - the width of the point spread function at half its maximum). The spatial resolution of the ECAT 953, using filtered backprojection to reconstruct images, is about 6mm FWHM in the x and y directions.
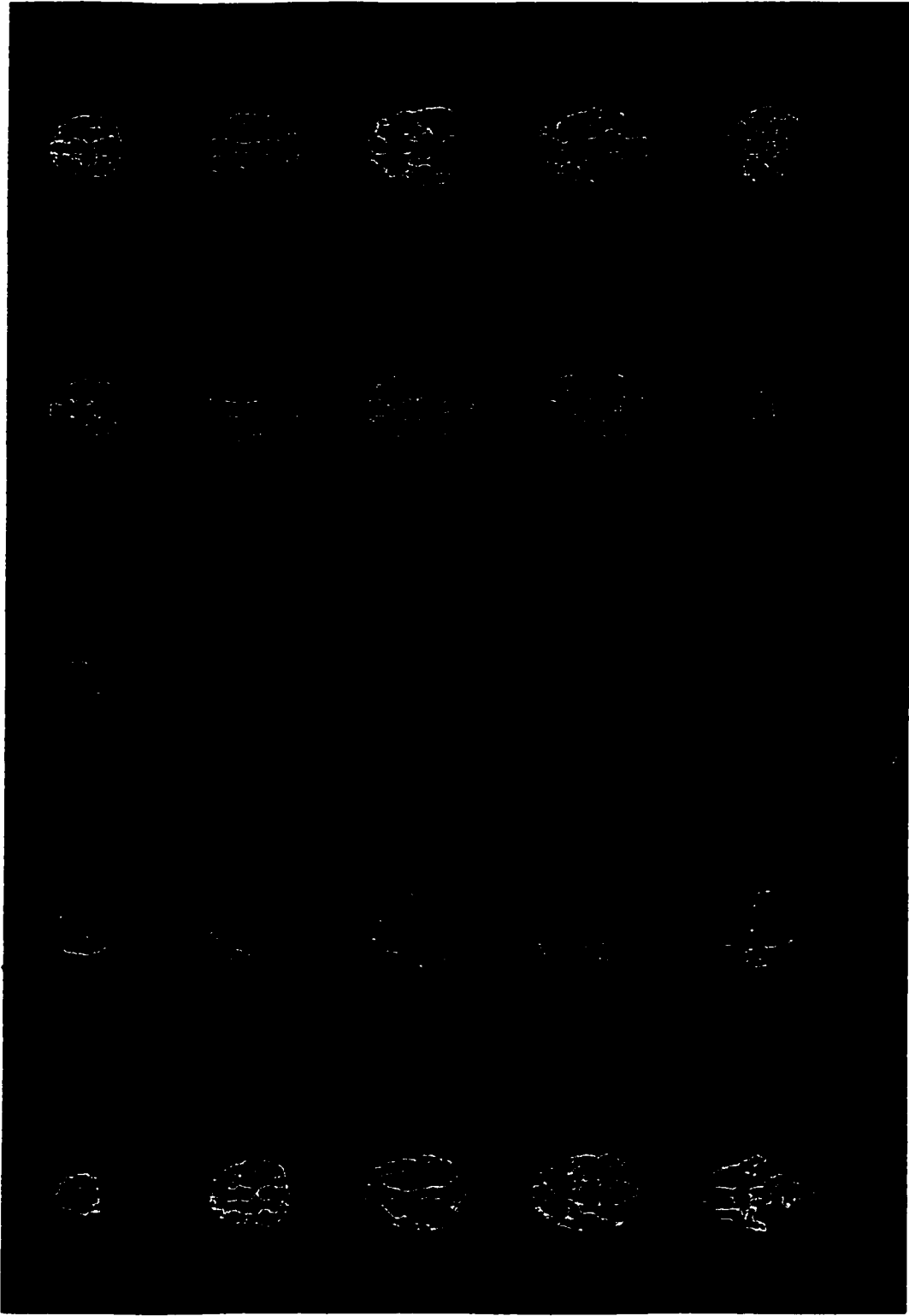
Figure 13. PET / [O-15]H2O Image of the Author's Brain Acquired During the Emotion Recognition Task

3.1.11. RADIOACTIVE ISOTOPES AND LABELLING

The great strength of PET lies in its ability to qualitatively and quantitatively image

the dynamic physiological and metabolic processes of the body. Four positron emitting

radioactive isotopes of particular value are Oxygen 15 (^{15}O), Carbon 11 (^{11}C), Nitrogen 13 (^{13}N)

and Fluorine 18 (^{18}F), with half lives of 2.07, 9.96, 20.4 and 109.7 minutes respectively (Ott

et al., 1988). These isotopes can be incorporated into biologically active compounds by

replacing like atoms with their radioactive unstable counterpart. Introduction of the labelled

compound into the body permits the imaging of tracer density and reflects metabolic

processes at work.

The ^{15}O-labelled water used in this study was obtained by irradiating ^{15}N with protons

and then passing the resultant radioactive oxygen gas through a hot oven and mixing it with

hydrogen to yield $H_2{}^{15}O$.

$$^{15}_{7}N + {}^{1}_{1}H \rightarrow {}^{15}_{8}O + {}^{1}_{0}n \qquad \rightarrow \qquad H_2 + \tfrac{1}{2}\,{}^{15}O_2 \rightarrow H_2{}^{15}O$$
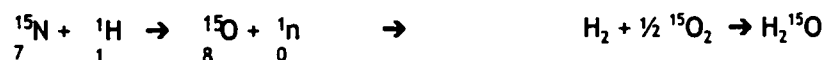
3.2 IMAGING BRAIN ACTIVITY

When assemblies of neurons in the brain change their level of activity, they require

energy to do so. The transmission of information from one nerve cell to the next is done

through a shift in the electrical membrane potential of the nerve cell and the release of

chemical neurotransmitters at the synapse. After a signal has been relayed the resting ionic

gradient between the inside and outside of the cell must be restored, thus requiring energy.

Under normal circumstances the brain uses glucose and oxygen as energy substrates in this

process. There are no substantial stores of these substrates in the brain, and therefore,

changes in metabolic activity are quickly followed by changes in local blood flow to restore

the supply of substrate. The close coupling of metabolic demand with changes in blood flow

permit PET measurements of regional cerebral blood flow to be used to explore the

functional anatomy of the human brain (Baron et al., 1982). Thus PET provides us with an

opportunity to view the regions of the brain activated by mental processes.

3.2.1. REGIONAL CEREBRAL BLOOD FLOW

Oxygen -15 PET is widely used to study changes in regional cerebral blood flow

(Brihaye et al., 1995). The short half life of ^{15}O (123 seconds) permits repeated

measurements with only a 7 to 10 minute washout interval between scans (to allow the

remaining residual radioactivity to decay). Although the diffusion of water across the blood

brain barrier is somewhat flow limited as compared to alcohols such as C-butanol, water is

generally considered freely diffusible (Herscovitch et al., 1987). In the $H_2^{15}O$ bolus protocol

the participant is positioned in the scanner and a transmission scan is acquired for use in the

attenuation correction procedures. An intravenous indwelling cannula is inserted into a

superficial vein (antecubital) of the right forearm and a saline drip started. A scan is

initiated with the recording of a 30 second background frame at the end of which the $H_2^{15}O$ is

infused over 5 to 10 seconds via the cannula. At this time a cognitive task may be presented

and scanning proceeds for a further 5 frames at 30 seconds per frame.

The $H_2^{15}O$ PET method has been shown to be highly sensitive to rCBF changes

especially during the initial phase of tracer uptake in the brain (Volkow et al., 1991). For this

reason, one group of researchers (Volkow et al., 1991) have suggested that the optimum

scanning time falls around 40 seconds after injection, while a second group (Kanno et al.,

1991) have proposed that the period between 90 and 120 seconds is best. Summing over frames 3, 4 and 5 of the scan covers the 30 to 120 second optimal scanning period.

3.3 THE PET PROCEDURE USED IN THIS THESIS

3.3.1. MULTISCAN STUDIES

The short half-life of ^{15}O and relatively low dose of radioactivity required for a single $H_2^{15}O$ PET scan make repeat scans in the same individual, in the same session possible (Raichle et al., 1983). Multiple scans are necessary because the changes in rCBF induced by neuronal activity are quiet subtle, with changes at most 10% around baseline levels. By pooling the data from a number of scans, statistical measures can be used to identify the differences in rCBF between, for example, rest and an activation task.

Activation studies are designed to locate the areas of the brain responsible for performing a certain cognitive process. Typically, a number of repeat scans are conducted on participants under two conditions, a baseline condition and an activation condition. It has been shown that three repeat measurements per task condition are sufficient to identify statistically significant differences in the results of O^{15} PET studies using tomographs with similar spatial resolution to ours (Mintun et al.,1989). The conditions must be carefully constructed such that they are similar in every aspect but differ only along the cognitive dimension being probed. It is assumed that under every condition similar neuronal activity would be associated with the participant's arousal level, their sensory experiences of the ambient lighting, sounds and smells, the pressure of the scanner bed against their back, any

motor activation required as part of the performance of the tasks and so on. Differences in localized rCBF between the two scans are then interpreted as indicators of regional neuronal activity specific to the activation task.

3.3.2. SCAN PROCEDURES USED IN THIS THESIS

Ethics approval for the two studies conducted in this thesis was obtained from the McMaster University Ethics Committee. Similar scan procedures were followed in both PET studies. An $H_2^{15}O$ PET protocol was used to identify changes in rCBF while participants completed a number of activation tasks. In the first study, participants solved some visual matching tasks, while in the second study participants were asked to match auditory and visual stimuli. Visual stimuli were presented on a computer monitor and auditory stimuli through earphones. Participants responded to the stimuli by pressing right and left hand-held response buttons.

A scanning session began with the arrival of a participant in the Nuclear Medicine Department, McMaster Medical Centre. The participant was asked to read and sign the study consent form (Appendix A) and a review of the PET procedure was provided. Female participants were required to complete a Pregnancy Screening form, and were tested within the first 10 days of the start of their menstrual cycle. While seated in front of the computer screen, the participant was given the response buttons (and ear phones in study #2) necessary for the activation tasks. A number of practice runs using stimuli similar to those of the experimental trials were presented to familiarize the participant with the task demands and assess his/her response speed. The instructions for the emotion matching trials in study #1 and #2 asked that participants match according to the emotions they saw and / or heard, and

did not specifically label the emotions in the task. Participants were told that during the study they might make some errors, but not to worry, it was more important that they attend and think about the stimuli. During the practice trials the experimenter was able to watch the computer display and in the second study, hear the auditory stimuli through a second set of ear phones. On the first practice trial in each of the experimental task sets, the computer presentation was stopped, and the experimenter reviewed the task demands with the participant, to ensure he/she understood what was required. The remainder of the practice trials were monitored by the experimenter. Prior to the presentation of the experimental trials, it was necessary for the participants to perform the practice matching tasks within a criterion response speed of 3 seconds per trial. All participants were able to meet this criterion.

In the second study, involving the young adults with autism, all participants watched a video in the periods between each scan in the series. The purpose of the video was simply to keep the participants entertained. Participants were provided with a selection of film titles from public television series NOVA and National Geographic. These films were selected because they are not highly charged with emotion. Particular care was taken to ensure that the film selection did not include a special interest or fixation for each participant in the group of participants with autism.

Regional cerebral blood flow was measured by the method of Lammerstma and Mazoyer (1990). The tomograph was an ECAT 953/31 from which the interplane septa had been removed to improve the sensitivity of the tomograph. With the participant lying comfortably on the bed of the tomograph, an intravenous drip was started in the right antecubital vein. The participant's head was positioned with respect to the orbito-meatal

line, allowing the brain from the vertex to the cerebellum to be covered by the axial field of

view of the tomograph. A head strap and/or foam batting was used to gently hold the head

in a comfortable position. Participants were asked not to move during the study, and were

not spoken to for the duration of the examination, except for the necessary instructions just

before the start of each condition. Low ambient light and minimal background noise defined

the environment.

Just prior to the start of each scan 555 megabequerel of $H_2^{15}O$ were drawn at the

cyclotron and transported to the PET room, the instruction set for a block of trials was

displayed on the computer monitor, and the scan was started. At 30 seconds the 555 mega-

becquerel of $H_2^{15}O$ have decayed to approximately 466 megabecquerel ($15e^{-0.693}$ x 30 / 123)

of $H_2^{15}O$. The 466 megabecquerel of $H_2^{15}O$ in approximately 2 ml of saline were injected

through the IV port, and then flushed with 5 ml of normal saline. The experimental trials

were begun once the injection was completed. Each scan involved six data frames collected

for 30 seconds each, for a total scan time of 3 minutes.

A series of consecutive measurements of regional cerebral blood flow were obtained

in each of the participants (nine scans in study I and eight scans in study II). Each block of

trials ran for 3 minutes. Response latencies and errors were recorded by the computer.

Upon the completion of a block of trials, participants rested quietly for a period of

approximately 7 to 10 minutes until the next scan. In study II participants passed the time by

viewing the video television program.

Scan file data (sinogram) were summed across frames 3, 4 and 5, then reconstructed

using filtered back projection (Hann filter with a cut-off frequency of 0.3) to yield one image

per scan. These images were corrected for attenuation and assembled into an *.img* format

for presentation to the statistical analysis package.

Using the dosimetry estimates of Brihaye et al. (1995) for the $H_2^{15}O$ bolus method the

effective dose equivalent for ^{15}O-labelled water is 1.15 microsieverts/megabecquerel

($\mu Sv/MBq$). With the total administration of at most 4194 MBq of $H_2^{15}O$, the participants in

our studies were exposed to an effective dose of 4823 microsieverts. This figure is above the

average annual dose figures for individuals living in Ontario, which were 3300 microsieverts in

1985 (Neil, 1985). However, the total injected activity of 4194 MBq (or 3700 MBq in study II)

is well below the acceptable limit of 8700 MBq suggested by Brihaye et al. (1995).

3.3.3. STATISTICAL ANALYSIS

To identify regional changes in rCBF a voxel by voxel analysis is used, wherein

univariate techniques are applied to each voxel to create a statistical image. However,

conventionally there are three steps that must be taken to ready the scan images for this

analysis; these are: realignment, normalization and smoothing. The method used to prepare

the images in this thesis and to assess significant changes between different conditions was

that of Statistical Parametric Mapping (SPM 99), developed in the Wellcome Department of

Cognitive Neurology (Queen Square, London, UK), and running under Matlab 5 (Mathworks Inc,

Sherborn, MA).

3.3.3.1. REALIGNMENT

In studies with repeated scans for activation and baseline conditions, the participant

remains in the scanner for the full protocol, and the total time spent lying on the scanner bed

includes the time needed for each scan and washout period. Over the course of a

one to three hour scanning session, the participant can be expected to move slightly on the

scanner bed. While more restrictive restraint devices can be used, they may actually cause

discomfort to the participant and detract from the study. It is preferable to encourage

participants to remain motionless during the scan to avoid blurring the acquisition, and when

needed to use a strap drawn lightly across the forehead to serve as a reminder not to move.

Reconstructed images must be realigned (usually with reference to the first scan) to correct

for the translational and rotational movement of the participant's head. In the studies

presented in this thesis, the scans from each participant were realigned using the first scan

as a reference. Six parameters for this rigid body transformation were estimated using a

least squares approach (Friston et al., 1995).

3.3.3.2. STEREOTAXIC NORMALIZATION

No two brains are physically identical, although the basic gyral anatomy does not

change from individual to individual and the functional localization of processes to each gyrus

is relatively fixed (VanEssen et al., 1998). This variation in brain morphology across

participants means that it is possible for a single voxel located at the same image coordinates

in the images from two different participants to fall in completely different gyri (Woods,

1996). Some form of anatomical normalization is needed therefore, before an analysis of

images across participants on a voxel-by-voxel basis can be conducted. This process is

termed stereotaxic normalization and involves transforming each participant's brain image

into the space of a standard brain template so that the images for one participant conform to the same general morphology as the next. By using normalized images in analyses, findings can be reported according to their Cartesian coordinates within the standard space and results across studies can be compared.

A number of standardized reference systems and atlases have been developed including that of Talairach and Tournoux (1988) and that of the Montreal Neurological Institute (http://www.bic.mni.mcgill.ca/). Despite the fact that the Talairach coordinate system is based on the mapping of transverse slices through a single brain, it has become widely used in neuroanatomy and functional imaging research. The origin of the Talairach coordinate system is located at the midpoint of an imaginary line connecting the anterior and posterior commissures (the AC-PC line). Normalizing a PET image begins by locating a series of gross anatomical landmarks, like the ventricles and hemispheres, and then the location of the AC-PC line can be estimated by regression analysis. Once the Talairach origin and axes are located the point of origin is shifted and the axes rotated to match the standard Talairach template. Next the image is deformed about the origin to match the morphology of the Talairach brain by shifting the scale of the image in the axial directions using a three dimensional linear affine (Friston et al., 1995). The images in the present studies were transformed into the standard space of the Montreal Neurological Institute template used in SPM99.

3.3.3.3. SMOOTHING

To this point, the image has only been filtered during reconstruction, and it remains quite noisy. Smoothing reduces the noise in the images, however, at the cost of reducing spatial resolution. The changes in regional cerebral blood flow are expressed over spatial scales of several millimetres whereas noise has higher spatial frequencies. Where group effects are being studied, smoothing ensures that the changes in rCBF from participant to participant are assessed on the spatial scale at which local homologies in functional anatomy are usually expressed. Consequently, the realigned / normalized image is now smoothed to remove some of this noise. In analyses conducted in this thesis the smoothing was done using a Gaussian kernel of 15 mm (FWHM). Woods et al. (1992) have shown that increased smoothing results in substantial improvements in the mean and maximum alignment errors, and that the mean misregistration is of the order of 0.7 mm using such a kernel.

3.3.3.4. STATISTICAL PARAMETRIC MAPPING

Statistical parametric mapping is predicated on the concept of functional segregation or specialization and is used to localize regionally specific activity in the brain. A common study design found in studies using SPM, is cognitive subtraction. Here two cognitive tasks are formulated such that their difference identifies a separable cognitive component, and differences in regionally specific brain activity are reflective of a corresponding functionally specialized area. When images have been reconstructed, aligned within participant, normalized and smoothed, a voxel by voxel analysis can proceed contrasting the different task conditions. The comparison of task conditions assumes that the same voxel in each image has a value reflecting local neuronal activity in the same functional area in each participant.

This assumption, however, is tempered by the variability introduced by errors in realignment or anatomical normalization, and natural biological variability in functional specialization.

The expected effects are organized into a design matrix, in which each column corresponds to a condition that has been built into the experiment or some confound. Regionally specific activations are outlined in terms of differences among experimental conditions (an activation effect) and are specified using contrasts. To test hypotheses about regionally specific condition effects the significance of a contrast is assessed with the Student's t-test at each and every voxel, yielding a statistical parametric map (SPM {t}) (Friston et al., 1995-2). Statistical inferences are made about local peaks in the statistical parametric map that exceed a selected height threshold. The significance of each peak is estimated in terms of the probability that the peak height observed could have occurred by chance over the entire volume analyzed. The peaks are characterized in terms of their maximal value and their spatial extent and are interpreted as regionally specific effects attributable to the experimental condition being tested. In the studies conducted for this thesis, the design was a multi-subject repeated measures ANOVA. The height threshold was set at $p = .01$ and the threshold for identifying significant voxels within each peak was set at $p \leq .001$ (uncorrected). Although there are other possible methods of analysis, it has been shown that there is relatively little difference between methods in the interpretation of the results (Arndt et al., 1995).

Neuroanatomic location of significant voxels was identified according to the stereotactic atlas of Talairach and Tournoux (1988). In SPM '99 smoothed images are transformed using a standard reference brain from the Montreal Neurological Institute. To shift from this reference to the Talairach and Tournoux coordinate system, a conversion was

necessary. The matlab conversion program by Brett (Medical Research Council / Cambridge http://www.mrc-cbu.cam.ac.uk/Imaging/) was employed for this purpose.

The results reported in the next three chapters (Chapters Four, Five and Six) concern within-group analyses of studies I and II. For each group, these analyses permit the localization of the regional activity associated with the processing demands of the tasks used in each study. The inferences drawn in through these analyses pertain to the particular participants examined. In Chapter Seven, further analyses of studies I and II are carried out to examine differences between groups using a Random Effects analysis. This analysis permits the extension of inferences to the population from which participants have been drawn.

CHAPTER FOUR

4.1 STUDY I: VISUAL EMOTION PROCESSING IN MEN AND WOMEN

Our first study examined the distribution of regional cerebral blood flow during the processing of facial emotion in men and women. Although there are a number of functional studies of face emotion processing in the literature, none have examined facial emotion processing strategies in a group of men and in a group of women under the same experimental protocol. At the outset of this thesis, much of the available research had been conducted with either mixed sex or female study groups (e.g. George et al., 1993). It was considered important, therefore, to examine the emotion processing strategies of normal males before studying a clinical population of individuals with autism, in which the availability of participants would be largely restricted to males (given a male to female sex ratio of 4 to 1 for the syndrome). Furthermore, we wished to refine and replicate the results from previous reports under our own experimental conditions. In light of Kring and Gordon's (1998) recent evidence that the sexes react differently to certain emotions, the current study extended the number of emotions used beyond that employed by George et al. (1993), to include all six of the recognized "universal" emotions; happiness, sadness, anger, disgust, surprise and fear. Three experimental tasks were used in order to distinguish the processing specific to emotion recognition from the extraction of detailed face information, and the more elementary processes involved in the detection of faces.

4.1.1. STUDY I : VISUAL EMOTION PROCESSING IN FEMALES AND MALES

Hypothesis: With the recognition of facial identity we expect to find that both male and female study groups demonstrate increased activity bilaterally in the inferior temporal region, particularly in the fusiform areas. Under conditions that require the processing of facial emotion, we expect activation in areas included in the functional network linking the middle and superior temporal regions, amygdala, cingulate gyrus and inferior frontal cortices. The research conducted on female adults by George et al. (1993), leads to the suggestion that frontal activation in female participants will be observed bilaterally. Activation associated with facial emotion processing in males, in contrast, is expected to be more lateralized, and localized to the right.

4.1.2. PARTICIPANTS

The participants studied in our first study were 8 male and 8 female young adults recruited by flyer posted across the university campus. Sample sizes between 6 and 10 participants are considered appropriate in the PET rCBF research (Arndt et al., 1996). The mean age of the male and female study groups was 21 years (range 20 to 23 years) and 21 years (range 20 to 22 years), respectively. All of the participants were right handed; they did not endorse any drug or alcohol abuse, past history of brain injury or traumatic loss of consciousness, major psychiatric illness or neurological problems.

4.1.3. THE ACTIVATION TASKS

The visual stimuli were displayed on a video screen at a viewing distance of 40 to 50 centimetres. A new stimulus was presented every 5 seconds. Regional cerebral blood flow was mapped while participants performed the visual processing tasks. The computer program used

to display the activation tasks was MEL (Appendix C; Psychology Software Tools, Pittsburgh,

PA). Response latency and accuracy data were collected on each trial. The activation tasks

were presented three times in a block randomized order.

Figure 14.   Examples of Visual Stimuli for Face Detection, Identity Recognition and
               Emotion Recognition Trials

Example of a Face Detection stimulus

Example of an Identity Matching stimulus

Example of an Emotion Matching stimulus
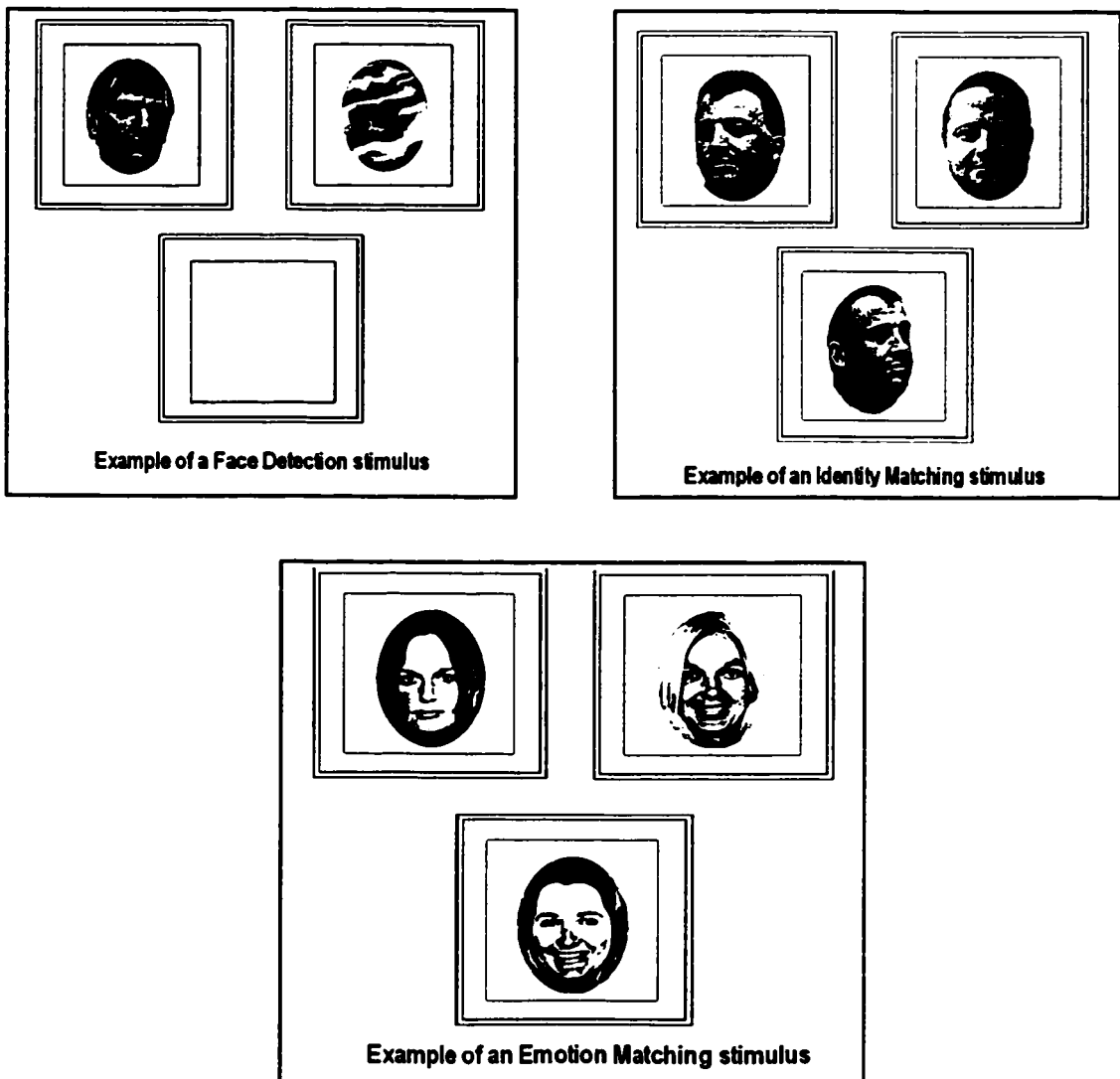
Participants viewed stimuli composed of three large white squares on a black background. A single target stimulus was presented centrally in the lower portion of the visual display while the two choice stimuli were located to the left and right of centre in the upper portion of the display. The photographs used in the emotion visual stimuli were selected from the standardized battery of Ekman and Friesen (1975) and conveyed the emotions: happiness, sadness, anger, fear, disgust and surprise. The nonsense patterns utilized in the face detection trials were similar to those employed by Haxby et al. (1994). Participants were asked to indicate which of the two choice stimuli matched the target stimulus by pressing hand held buttons with their right or left thumbs.

Activation data were collected while the participants performed three different matching to sample tasks: a facial emotions recognition matching task, and two control tasks involving an identity matching task and a face detection task utilizing faces and nonsense patterns of equivalent complexity. To remove background and non-facial cues like hair style and to force participants to focus on the features of the face, all of the face stimuli were matted with a grey oval cut-out. Care was taken in the selection of face stimuli to exclude faces with glasses, earings and other salient non-facial features. In the emotional matching task participants were instructed to match for emotional content and were not told what emotions to expect. The stimuli in each block of trials were balanced for the number of male/female faces presented, the number of trials depicting each of the six emotions and types of emotion appearing in the incorrect choice position. In the identity matching task the photographs were of neutral faces in which the orientation of the faces differed between the target and the correct choice stimulus. The incorrect choice stimulus was of a different face. Again the trials in each block were balanced for the number of male and female faces

presented. The face detection task required that participants indicate the presence of a face (neutral) in either the left or right top positions. The incorrect choice in this task was created by grossly distorting the face pictures to form un-namable oval nonsense patterns similar in appearance to the control stimuli used in prior studies (Haxby et al., 1994).

4.1.4. RESULTS

4.1.4.1. BEHAVIOURAL DATA

The response latency and error data of participants for each task were analyzed using repeated measures analyses of variance, (ANOVAs) with the within subjects factors identified as blocks and trials, and the between subjects factor identified as group (male or female). The results of these analyses are summarized in Appendix D. There were no significant differences between the error rates of male and female study groups in any of the three activation tasks (see Table 1).

Table 1.
Mean Response Latencies and Percent Correct to the Activation Tasks,
and Group Comparisons using Repeated Measures ANOVAs

Task	Response Latencies (msec)			% Correct		
	Males Mean ±sd	Females Mean ±sd	ANOVA Between Subject Effects F(1,14) p	Males Mean	Females Mean	ANOVA Between Subject Effects F(1,14) p
Detection	763 ±154	748 ±201	0.030 0.864	99 ±0.4	99 ±0.4	0.000 1.00
Identity	1371 ±166	1421 ±235	0.122 0.732	97 ±2.1	98 ±0.8	2.386 0.15
Emotion	2039 ±178	2160 ±217	1.085 0.315	88 ±3.2	90 ±4.2	0.951 0.35

Furthermore, the response latencies of males and females were not significantly

different for the detection task, the identity recognition task, or the emotion recognition task

(Table 1). A significant within subjects effect for blocks (F (2, 28) = 12.174, p < 0.001) was

identified for the response latencies to the detection trials. The within subjects factors,

blocks and trials, for the latencies to identity trials, showed significant effects (block F (2, 28)

= 7.547, p < 0.003; trials F (35, 490) = 5.606, p < 0.001). Similarly, the within subjects factors

for the errors to identity trials showed significant effects for blocks (F (2, 28)= 6.142,

p < 0.016) and trials (F (35, 490) = 14.841, p < 0.001). The within subjects factors for the

latencies to emotion trials showed significant effects for blocks (F (2, 28) = 5.348, p < 0.012)

and trials (F (35, 490) = 13.746, p < 0.001). In addition, the within subjects factors for the

errors to emotion showed a significant effect for blocks (F (2, 28)= 7.968, p < 0.003) and

trials (F (35, 490) = 8.428, p < 0.001). These findings indicate that there was a change in the

participant's latencies and errors across the blocks, and differences from one trial to the next

in the latencies and errors recorded for the emotion and identity tasks.

Chart 1. Study I: Mean Response Latency of Face Detection, Identity Recognition
and Emotion Recognition
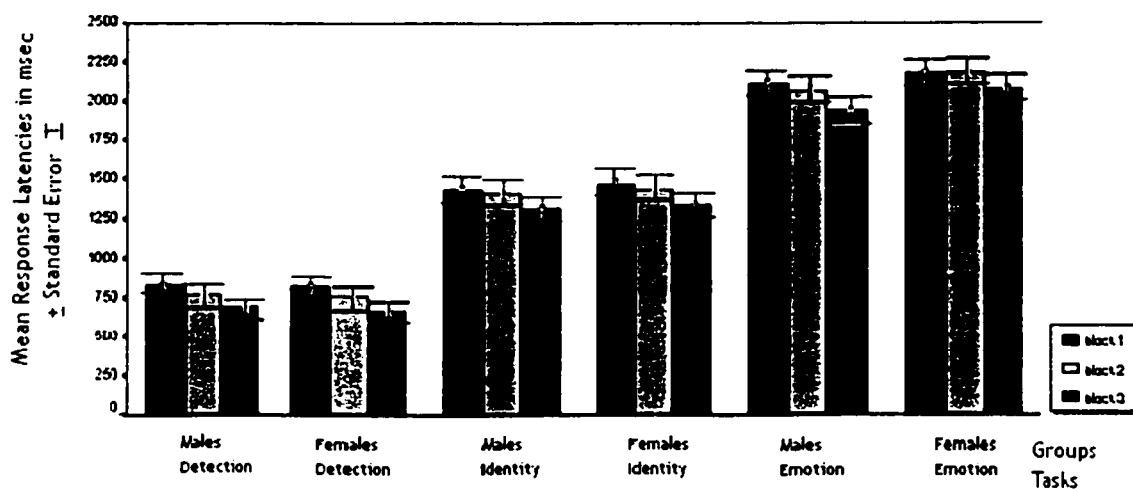
Chart 2. Study I: Mean Percent Correct for Face Detection, Identity Recognition and Emotion Recognition
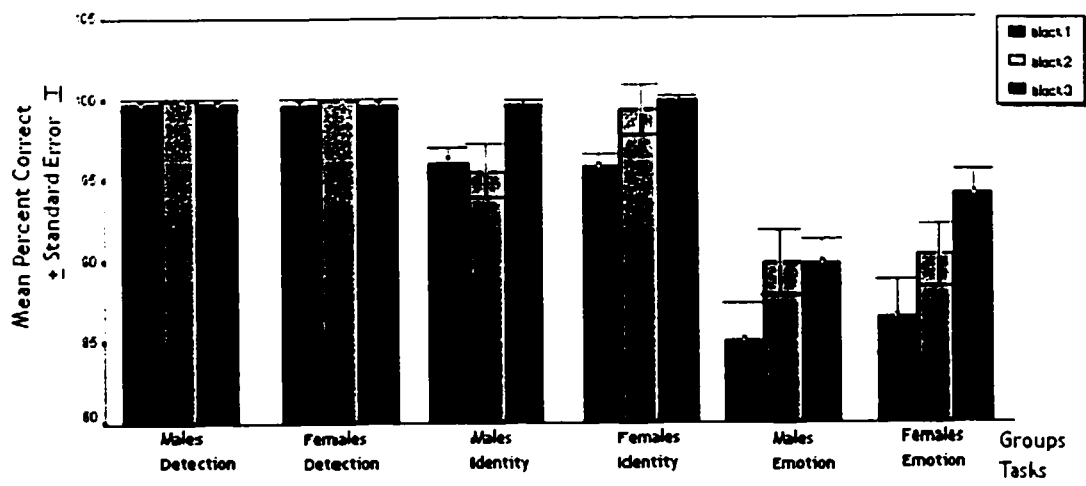
The Charts 1 and 2 demonstrate that the participants' response latencies and errors decreased over the task blocks.

Paired *t*-tests comparing the mean response latency and error data between task conditions for each study group (see Table 2), identified that both study groups were faster and made fewer errors on detection trials, as compared to both identity matching trials and emotion matching trials. Furthermore, both study groups were faster and made fewer errors on identity matching trials as compared to emotion matching trials.

Table 2.

Paired Comparisons of Activation Task Performance of Each Study Group

	Activation Tasks Compared	Paired Comparisons of Response Latencies		Paired Comparisons of % Correct	
		$t(7)$	p	$t(7)$	p
Males	Identity vs Detection	11.49	p< 0.001	4.15	p<0.005
	Emotion vs Detection	21.27	p< 0.001	9.99	p< 0.001
	Emotion vs Identity	19.33	p< 0.001	6.84	p< 0.001
Females	Identity vs Detection	12.16	p< 0.001	5.62	p< 0.002
	Emotion vs Detection	15.23	p< 0.001	6.67	p< 0.001
	Emotion vs Identity	11.02	p< 0.001	6.70	p< 0.001

Comparisons of the response latencies to each emotion presented in the emotion recognition trials revealed no differences in the response speeds of males and females across each emotion type (see Table 3). Similar comparisons of the percentage correct for each emotion identified that males made more errors matching angry faces than females. No other differences were identified between the error rates of males and females to the remaining emotion types (Table 3).

Table 3.
Mean Response Latency and Percent Correct to Each Emotion Type
and a Comparison of Male and Female Mean Values

Emotion	Performance Data	Males mean ±sd	Females mean ±sd	Comparison of Male and Female Means $t(14)$	p
Happy	Response Latency	1619 ±214	1695 ±191	0.75	p > 0.46
	% Correct	98 ±3.1	99 ±2.7	0.51	p > 0.61
Sad	Response Latency	2217 ±289	2199 ±240	0.14	p > 0.88
	% Correct	87 ±5.7	85 ±7.7	0.40	p > 0.69
Fear	Response Latency	2184 ±244	2202 ±181	0.17	p > 0.86
	% Correct	85 ±8.1	86 ±5.1	0.40	p > 0.69
Anger	Response Latency	2292 ±233	2346 ±290	0.41	p > 0.68
	% Correct	78 ±5.1	86 ±10.5	2.03	p < 0.07
Disgust	Response Latency	1841 ±227	2052 ±293	1.61	p > 0.12
	% Correct	86 ±8.2	90 ±5.2	1.05	p > 0.31
Surprise	Response Latency	1899 ±220	1970 ±220	0.65	p > 0.52
	% Correct	96 ±4.2	96 ±4.0	0.23	p > 0.82

4.1.4.2. ACTIVATION DATA

The results from paired contrasts (Table 4) conducted with SPM '99 are presented

below. At this stage, within group analyses are presented in order to explore the strategies

employed by each group to perform the tasks. The t-test and p values are at the voxel level and

the illustrations display the result of comparisons conducted using a height thresholds of 0.001

and 0.01 (Figure 15).

Figure 15.   Key to Activation Images

■ Height Threshold set at p = 0.001

▣ Height Threshold set at p = 0.01
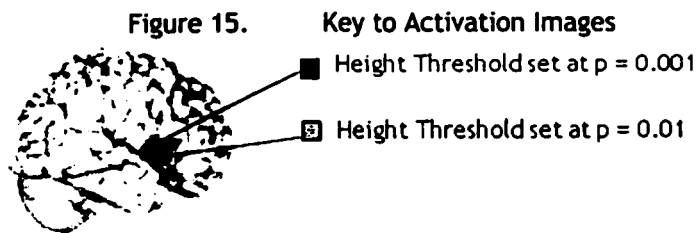
Table 4. The Identification of Activation Results through Paired Contrasts

	Contrast	Activation revealed
Facial Identity	*Facial Identification - Facial Detection*	to identify the activation during facial identity matching and control for facial detection.
Facial Emotion	*Facial Emotion - Facial Detection*	to identify the activation during emotion matching inclusive of the processing of facial features, and control for face detection.
Visual Emotion Recognition	*Facial Emotion - Facial Identification*	to identify the activation during emotion matching and control for the activation seen with facial stimuli or viewing faces as objects.

4.1.4.3. FACIAL IDENTITY (IDENTITY - BASELINE DETECTION)

The rCBF pattern produced when female participants performed identity matching (contrasted with baseline face detection: see Figure 16) revealed activity located medially and spreading bilaterally in the lingual gyrus, at the left anterior temporal pole, the right superior occipital gyrus and the left occipital cuneus.

Figure 16. Female Participants Identity Recognition
Areas of significant increase in rCBF during Identity recognition trials as compared to baseline face detection trials

left sagittal right sagittal posterior coronal anterior coronal

ventral transverse dorsal transverse

1. lingual gyrus
2. left anterior temporal pole
3. right superior occipital gyrus
4. left occipital cuneus
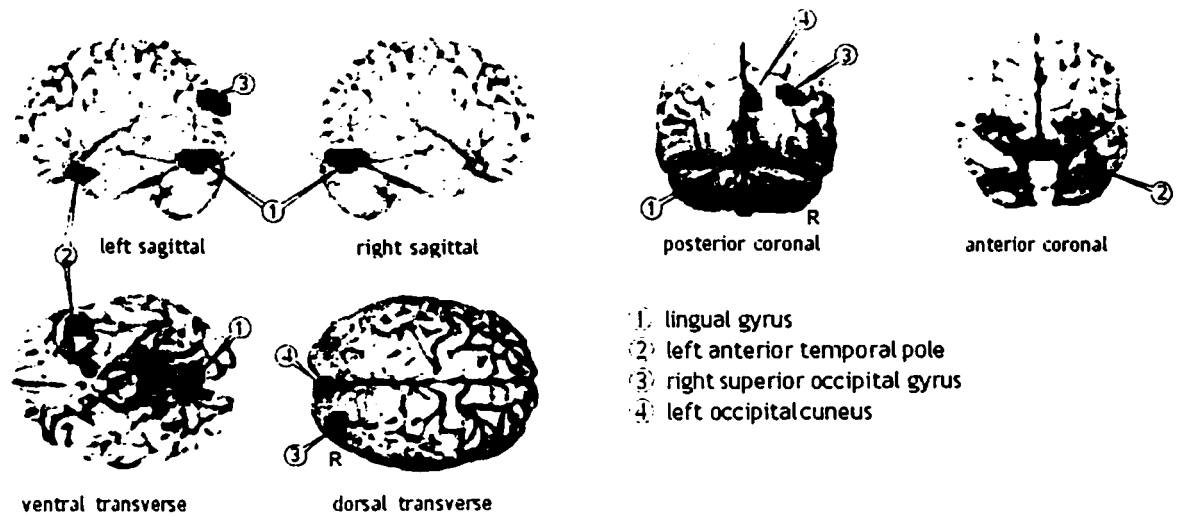
The same contrast for male participants identified the fusiform gyri, bilaterally, as the most significant areas of activation (Figure 17).

Figure 17. Male Participants Identity Recognition
Areas of significant increase in rCBF during Identity recognition trials as compared to baseline face detection trials

left sagittal right sagittal posterior coronal anterior coronal

ventral transverse dorsal transverse

1 2 fusiform gyri
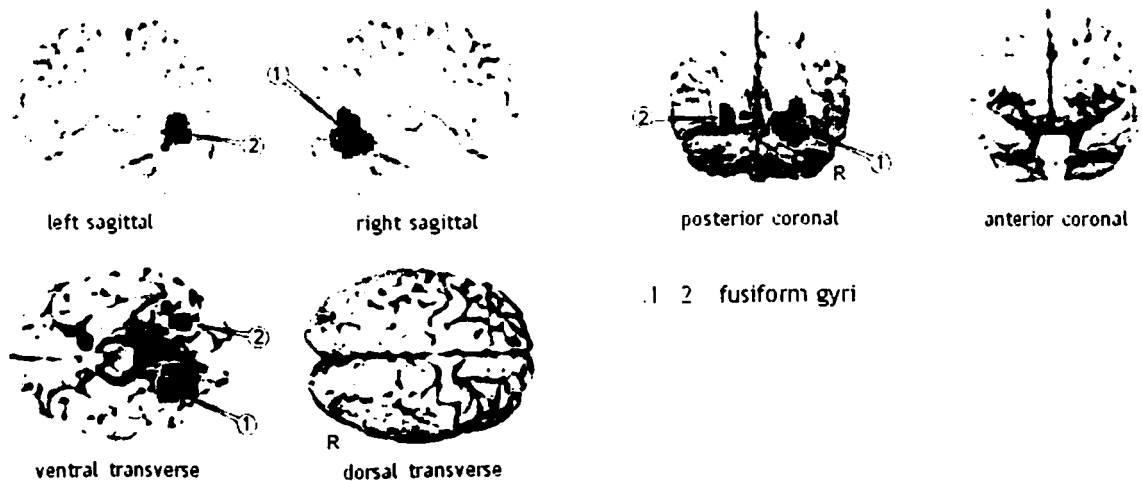
4.1.4.4. FACIAL EMOTION PROCESSING (EMOTION - BASELINE DETECTION)

Contrasting the emotion matching trials with the baseline face detection task identified

significant activation in the right and left lingual gyrus, the left inferior occipital gyrus and the

pulvinar region of the thalamus for the female participants (Figure 18).

Figure 18. Female Participants Facial Emotion Processing:
Areas of significant increase in rCBF during Emotion Recognition trials as compared to Baseline face detection trials

left sagittal   right sagittal

posterior coronal   anterior coronal

ventral transverse   dorsal transverse

①② lingual gyri

③ left inferior occipital gyrus

④ thalamus
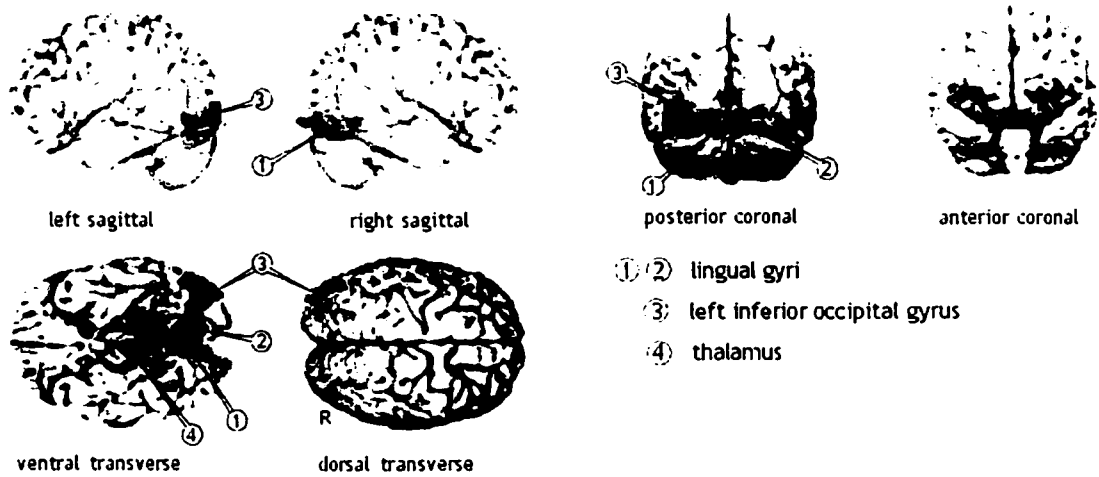
Contrasting rCBF on emotion trials with that for detection trials for the male data identified

activation in the left fusiform gyrus, the right precentral gyrus and the right inferior parietal lobe

(Figure 19).

Figure 19. Male Participants Facial Emotion Processing:
Areas of significant increase in rCBF during Emotion Recognition trials as compared to Baseline face detection trials

left sagittal   right sagittal

posterior coronal   anterior coronal

ventral transverse   dorsal transverse

1 left lingual gyrus
2 right precentral gyrus
3 right inferior parietal lobe
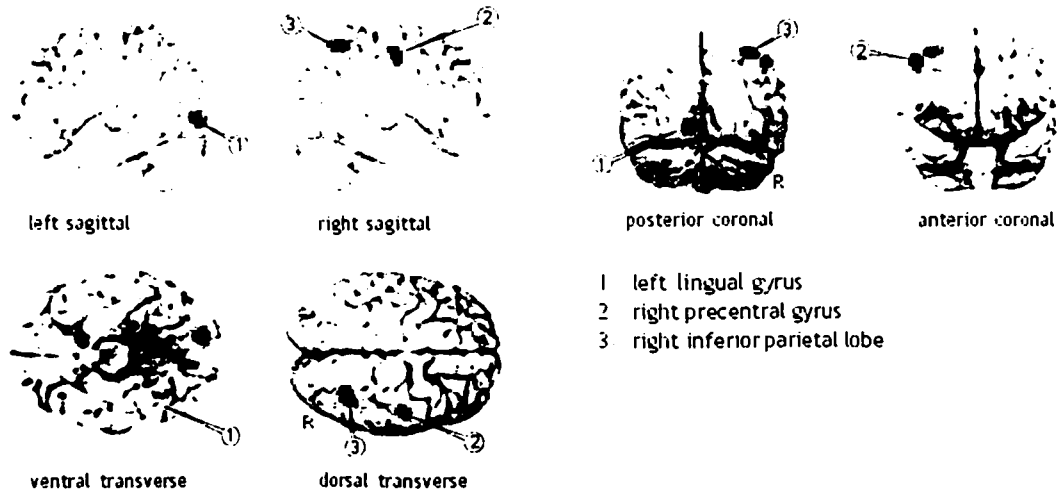
4.1.4.5. Facial Emotion Recognition (Emotion - Identity)

Contrasting the rCBF for emotion matching with that for the identity matching trials for

female participants revealed activity in the right inferior frontal gyrus, the left middle frontal gyrus,

the right inferior occipital gyrus, and the right middle temporal gyrus (Figure 20).

Figure 20. Female Participants Emotion Recognition :
Areas of significant increase in rCBF during Emotion Recognition trials as compared to Identity Recognition trials

left sagittal   right sagittal   posterior coronal   anterior coronal

ventral transverse   dorsal transverse

① right inferior frontal gyrus
② left middle frontal gyrus
③ right inferior occipital gyrus
④ right middle temporal gyrus
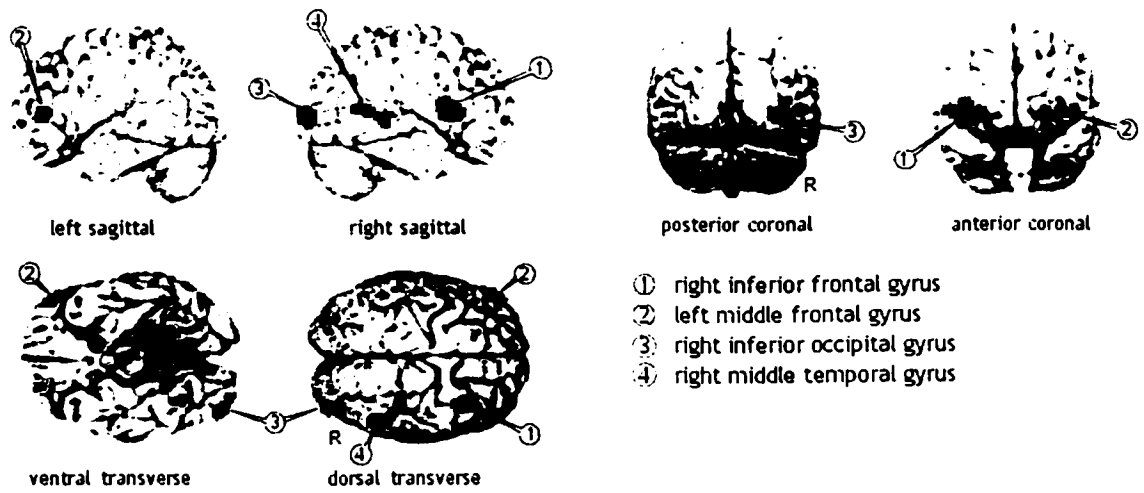
Contrasting the emotion matching with identity matching trials for male participants revealed

activity in the right inferior frontal gyrus (Figure 21).

Figure 21. Male Participants Emotion Recognition :
Areas of significant increase in rCBF during Emotion Recognition trials as compared to Identity Recognition trials

left sagittal   right sagittal   posterior coronal   anterior coronal

ventral transverse   dorsal transverse

I right inferior frontal gyrus
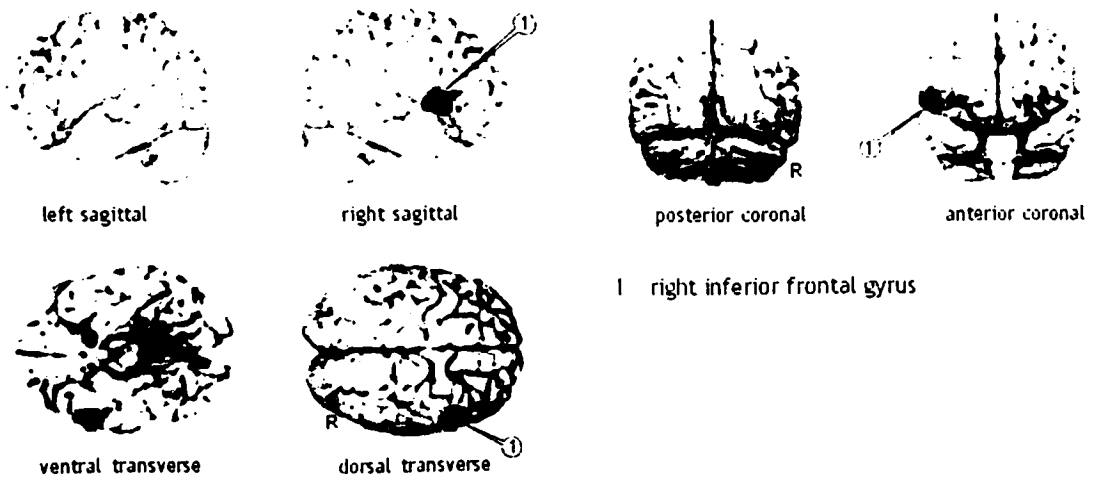
Table 5.

Regions of Significant Change in Regional Brain Activity
Identified through Contrasts of the Experimental Conditions

Contrast	Sex	Brain Location	Talairach Coordinates x,y,z (mm)			Brod mann Area	t value	p value
Identity Recognition (I - D)	F	L lingual gyrus	- 4	-68	-11	18	3.78	p < 0.001
		L temporal pole (STG)	-47	22	-22	38	3.61	p < 0.001
		R superior occipital gyr	31	-74	31	19	3.37	p = 0.001
		R occipital (cuneus)	2	-86	26	18/19	3.19	p = 0.001
	M	R fusiform gyrus	30	-49	-16	37	4.51	p < 0.001
		L fusiform gyrus	-23	-60	-5	37/19	3.97	p < 0.001
Emotion with face processing (E - D)	F	L lingual gyrus	-10	-74	-16	18	3.79	p < 0.001
		R pulvinar	8	-25	-4		3.81	p < 0.001
		R lingual gyrus	8	-72	-8	18	3.36	p = 0.001
		L inferior occipital gyr	-37	-91	3	18	3.49	p = 0.001
	M	L lingual gyrus	-14	-81	2	18	3.31	p = 0.001
		R precentral gyrus	51	0	42	6	2.92	p = 0.003
		R superior parietal lobe	41	-50	55	7	2.88	p = 0.003
Emotion Recognition (E - I)	F	R inferior occipital gyr	43	-88	8	18	3.61	p < 0.001
		R inferior frontal gyr	38	24	4	45	3.42	p = 0.001
		R middle temporal gyr	51	-50	12	22	3.41	p = 0.001
		L middle frontal gyrus	-49	47	5	46	3.17	p = 0.001
	M	R inferior frontal gyrus	56	16	2	45	4.51	p < 0.001

4.1.5. DISCUSSION

4.1.5.1. FACIAL IDENTITY RECOGNITION (Identity - Detection)

The observation of inferior occipito-temporal activation with identity recognition is consonant with previous research. The location of the activation with identity matching for our female participants is more medial than that reported in some previous studies. However, both George et al. (1993) and Sergent, Ohta and Macdonald, (1992) reported broader activation of the inferior occipito-temporal area with identity recognition, including midline activation similar to the results for our female participants. In addition, lingual and fusiform activation has been identified in a familiar face recognition task (Andreasen et al., 1996). Finally, Puce et al. (1995) reported fMRI activation in the lingual gyri with the presentation of scrambled faces and noted that activation here was medial to the activation found with the presentation of faces. They suggested the lingual area was concerned with the visual processing of stimuli with high spatial frequencies and complex patterns. As fusiform activation has been reported when participants passively view face stimuli (Puce et al., 1995; Kanwisher, McDermott and Chun, 1997; Sams et al., 1997), it may be suggested, that the use of face detection as the baseline task in the present study may have produced fusiform activation which was subtracted away as a result of the comparison process. The remaining activation, then, may reflect greater visual processing associated with identity processing.

This suggestion is supported by the activation of the occipital gyrus for the female participants, possibly reflecting increased visual processing demands. Here again we find that in similar studies where tasks have required more than the passive viewing of faces, broader activation is noted. For example, George et al. (1993) identified a ventral occipital response

bilaterally during facial identification. Furthermore, Andreasen et al. (1996) identified that among other regions the cuneus / precuneus area was activated during gender discrimination, and suggested that this area may function as a storage or reference region.

The final area in which the identity recognition data for our female participants showed significant activation was the left anterior temporal pole. On the basis of electrophysiological recordings of ventral temporal region, Allison et al. (1994) have suggested that while the fusiform region may be involved in the early processing of facial features, the mnomic and associative processing of face information occurs later, downstream in the anterior temporal poles. In this regard, Sergent, Ohta and Macdonald (1992) suggested that the anterior temporal poles were the depository of information about individuals and unique entities after finding significant activation in this area when participants were asked to classify famous faces. However, functional neuroimaging studies have not only associated activation of the anterior temporal cortex with familiar face identification (Sergent, Ohta and Macdonald, 1992) but also visual discrimination tasks performed on faces and words (Gorno Tempini et al., 1998), object naming (Price et al., 1996), object categorization (Moore and Price, 1999) and the classification of subordinate relative to basic categories of objects (Gauthier et al., 1997). Common to these tasks is the requirement to utilize semantic and perceptual knowledge to differentiate between similar objects and categorize them. In all, activation of the anterior temporal pole would suggests that our female participants had processed the face identity pictures quite thoroughly and may have begun to develop some learned associations. The identity recognition stimuli were constructed from a photographs taken from a number of angles, on a limited number of individuals. Given the fact that photographs of the same individuals would re-occur, it is possible that we may have encouraged participants to start drawing associations and linking

faces.

In males, the significant rCBF pattern replicated previous research identifying bilateral activation of the fusiform gyrus with passive face viewing (Puce et al., 1995; Kanwisher, McDermott and Chun, 1997) and identity matching (Haxby et al., 1994; George et al., 1993). Inspection of the data for our male participants revealed that the activation of the fusiform gyrus encompassed a larger area on the right (1616 voxels) than on the left (344 voxels). This pattern is consistent with past research demonstrating bilateral fusiform activation with face processing tasks, and a pattern of greater activation on the right than left (Haxby et al., 1994). It is also consistent with the notion of a right hemispheric advantage in processing face stimuli (Dubois et al., 1999).

4.1.5.2. FACIAL EMOTION PROCESSING (Emotion - Detection)

Contrasting the rCBF measured during our baseline detection task with that recorded for emotion recognition trials identifies brain regions that are activated when participants examine faces as objects and process emotional information. In the present study, inferior temporal activations were identified in the data of our female participants. Thus relative to the baseline task in which there was little demand to process the face stimuli, the greatest activations seem to reflect the face processing demands of the emotion task. For female participants the activation was bilateral, and though the local maxima were found in the lingual gyri, the activation spread laterally to include the fusiform areas. These observations complement the report of broad activation of this area, including fusiform and lingual gyrus in MEG data for emotion recognition by Streit et al. (1999). The second area of significant activation identified

in the female data (emotion - detection) was the inferior occipital cortex. Some studies of

facial emotion have identified additional occipital activation, relative to baseline measures.

For example, the study by George et al. (1993) contrasted the activation for emotion

recognition trials with that of spatial location trials and identified significant bilateral activity

in the occipital cortex. Similarly, Phillips et al. (1997) recorded increases in the activity of the

occipital cortex with the presentation of facial expressions of sadness. With regard to the

present findings, it may be suggested that the emotion task placed greater demands on the

processing of visual detail, and that this resulted in greater neuronal activity in the visual

association areas. However, the visual association areas receive extensive cortical projections

from the amygdala, and it has been suggested that the amygdala may play a role in modulating

sensory processing in accordance with the affective state of the individual (Aggleton, 1993).

Thus it is suggested that the amygdala is active in both attaching emotional significance to the

sensory experience and guiding, evaluating and preparing the sensory association areas to

respond to emotionally arousing sensory stimuli (Reiman et al., 1997; Dubois et al., 1999).

With reference to the present study, this suggestion would be far more convincing if we

had identified amygdalar activation too. And yet, the third significant region of activation in

the female data (Emotion versus Detection) was the thalamus. Similar to occipital areas,

thalamic activation has been reported in a number of functional studies on emotion (Reiman et

al., 1997; Phillips et al., 1997; Lane et al., 1997). Thalamic activation was demonstrated by

Phillips et al. (1997) with the presentation of face stimuli conveying high intensities of disgust.

They attributed these findings to the activation of a limbic circuit connecting the orbito-frontal

cortex, the ventral striatum and thalamus and suggested that these regions participated in the

generation of an emotional response to visceral, offensive stimuli. However, Lane and

associates have also reported thalamic activation with the presentation of films designed to elicit feelings of happiness, sadness and disgust, and suggested that the thalamus participated in a more general emotional response that was not specific to a particular type or valence of emotion (Lane et al., 1997; Reiman et al., 1997). These finding would suggest that, in comparison to the study by George et al. (1993) in which happy and sad face stimuli were used, the use of a larger range of emotional stimuli in the present study led to the activation of a wider network of functionally related regions associated with emotion processing.

The facial emotion comparison (Emotion minus Detection) for the male participants, revealed significant changes in regional brain activity in the inferior temporal area which was confined to left hemisphere and not as broadly distributed as that demonstrated in the female data. An additional area of activation was noted in the right superior parietal lobe. This finding may reflect increased attention demands during emotion processing, as lesion studies have associated parietal damage with disorders of attention and arousal (Mesulam, 1999: Karatekin, Lazareff and Asarnow, 1999). This suggestion is further supported by PET rCBF data demonstrating that this area participates in both space-based and object based attention (Fink et al., 1997). Increased processing and attention demands with emotion processing are also suggested by our observations of longer reaction times and greater errors on emotion trials for our male participants as compared to their performance on the detection trials.

4.1.5.3. FACIAL EMOTION RECOGNITION (Emotion - Identity)

Contrasting the rCBF recorded during the facial emotion task with that recorded for the identity recognition task essentially removes the activity associated with the extraction of detailed facial information and leaves behind the activation specific to the processing of facial

emotion. Bilateral activation of the frontal cortices was identified in our female data.

On the right, the activity was localized within the inferior frontal region, while on the left, the

activation was identified in a slightly more anterior location in the middle frontal gyrus.

The left inferior frontal activation, although somewhat more ventral, is similar to that reported

by George et al. (1993) and the right activation (at coordinates 38, 24, 4) is near a region

reported by Blair et al. (1999) when participants viewed facial emotion pictures depicting

sadness. In addition, the observation of bilateral frontal activation for our female participants

is consistent with the findings of George et al. (1993) in their study of a group of female

participants.

Significant activation was also identified in the middle temporal gyrus (bordering the

superior temporal sulcus) of our female participants. Physiological studies in macaques have

identified that cells in the superior temporal sulcus are selectively active for facial expression

(Hasselmo, Rolls and Baylis, 1989), or, head orientation or direction of gaze (Perrett et al.,

1991). In humans, bilateral lesions to this area result in deficits in gaze discrimination, and yet

leave face identity matching capacities intact (Heywood and Cowey, 1993). Studies of emotion

recognition have reported middle and superior temporal gyrus activation during the

presentation of stimuli showing facial expressions of disgust (Phillips et al., 1997), and sadness

(Blair et al., 1999). In women, recall of personal experiences and film induced happiness and

sadness (but not disgust) have also resulted in significant activation of the middle temporal

gyrus (Lane et al., 1997). Finally, the MEG study by Streit et al. (1999) identified middle

temporal cortex activation during the processing of facial emotion. It has been suggested that

because this area is richly connected to both visual streams (Ungerleider and Mishkin, 1982) it is

well suited to assist in the analysis of complex facial information, especially during the

recognition of emotional expressions (Streit et al., 1999). The observation of temporal

activation in the present study, as well as activation of the occipital pole, would suggest that

our female participants engaged in a more thorough visual analysis of the stimuli, relative to

the identity recognition trials.

For our male participants, significant activation was recorded solely in the right inferior

frontal gyrus. Bilateral activation was not identified for males and this seems to support the

view that emotion recognition is more strongly lateralized in males. Narumoto et al. (2000)

have recently reported right inferior frontal activation for a group of male and female

participants when facial emotion matching was contrasted with a baseline facial gender

recognition task. These findings add to the growing body of evidence suggesting that the right

inferior frontal region plays an important role in facial emotion recognition (Nakamura et al.,

1999).

As compared to the results for the male participants, the observation of activation in the

right occipital, right temporal and bilateral frontal regions in female participants is consistent

with the suggestion that women are more likely to have greater distribution and less

lateralization of function than males (McGlone, 1980; Kimura and Harshman, 1984). It may also

suggest that female participants found the emotional stimuli more engaging than their male

counterparts and as a result conducted more detailed analysis of the visual features on emotion

trials.

An alternate explanation of these results is raised by the hypothesis that the brain

organizes emotion as a function of valence, with the right hemisphere specialized for negative

emotions and the left for positive emotions. If we compare this study with that of George et al. (1993), we find that the presentation of happy and sad facial emotions to female participants resulted in bilateral (greater left than right) inferior frontal activation. Thus, it might be suggested that the presentation of a balanced number of positive and negative emotional stimuli resulted in the activation of both hemispheres. If we examine the stimuli employed in the present study, we find that the 6 universally recognized emotions are unevenly distributed with (conceivably) more negative emotions (sad, angry, disgust, fear) than positive emotions (happiness, surprise). It is plausible that the greater number of 'negative' stimuli resulted in greater activation on the right, especially for males. However, if this were the case, we might not expect to see a bilateral response in our female data. Furthermore, previous research employing facial emotion stimuli have, on the whole, identified bilateral distributed activations (George et al., 1993; Phillips et al., 1997; Morris et al., 1996). One exception is the PET study by Blair et al. (1999) which examined responses to sad and angry faces, and identified primarily right sided activations. Unfortunately, the study group in this study was all males, and so we cannot resolve whether the right sided activation pattern was due to the sex of the study group or the valence of the emotions explored.

Another plausible account of the current findings may lie in the extent to which the two study groups verbally labelled the emotion stimuli. Bowers et al. (1985) have suggested that the left and right hemispheres participate in labelling facial expressions with the left providing the storage of verbal knowledge of emotion and the right storing non-verbal knowledge of emotion. It may be suggested, that our female group engaged the left hemisphere (as well as the right) because they tended to verbally label the emotional stimuli, whereas, our males may have relied more on the visual aspects of the stimuli and therefore solely engaged the right

hemisphere. However, recently, Narumoto et al. (2000) identified bilateral activation of the frontal cortices with facial emotion recognition, when the use of verbal processing strategies were controlled for. In this study, a mixed group of male and female participants were presented with a delayed matching task in which the target stimulus was either a word (eg. SAD) or a picture of a facial emotion, and the choice stimuli were two pictures of facial emotion, one of which matched the emotion of the target stimulus. Significant activation was reported bilaterally in the frontal cortices (BA 10 and BA 46) when emotion recognition trials using facial target stimuli were contrasted with those using verbal target stimuli. These findings identify that bilateral frontal activation may be observed for facial emotion matching when the effects of verbally labelling the stimuli are removed. With regard to our study, Narumoto et al.'s (2000) findings suggest that differences between male and female activation patterns during emotion matching are not necessarily the result of the female participants' use of verbal labelling, and strengthen the argument that they engaged a wider functional network with the processing of emotion.

4.1.6. CONCLUSION FOR STUDY I

To examine the functional localization of regions that participate in the processing facial emotion we measured regional cerebral blood flow in eight male and eight female young adults using $H_2{}^{15}O$ PET. Three tasks were presented to the participants, a face detection task, an identity recognition task and an emotion recognition task. Paired contrasts of the changes in the regional cerebral blood flow associated with each of these tasks identified areas of significant activation associated with identity recognition and facial emotion recognition.

The recognition of facial identity, as compared to face detection, resulted in significant bilateral activation of the fusiform gyri in male participants, and, bilateral activation of occipital and lingual areas in our female participants. These findings were considered consistent with a growing body of evidence identifying areas of the inferior occipito-temporal region as functionally specialized for the processing of faces.

Significant activation was observed in the right inferior frontal cortex of males with the recognition of facial emotion, as compared to facial identity matching. In our female participants, facial emotion recognition was associated with significant activation of the frontal cortices bilaterally, the right middle temporal gyrus and the right inferior occipital gyrus. Activation in these areas is in keeping with the results of previous functional imaging studies on emotion processing. Furthermore, it is suggested that these findings reflect sex differences in the functional localization of emotion processes. The activation of a wider distributed network by females is consistent with research identifying that some cognitive processes are more distributed and less lateralized in females than males.

CHAPTER FIVE

5.1 STUDY II: CROSS-MODAL EMOTION RECOGNITION

The purpose of our second study series was two-fold. First, we wished to expand on the research conducted in our first study by identifying the changes in regional cerebral blood flow associated with cross-modal emotion recognition in male and female participants. Second, we wished to examine changes in rCBF with cross-modal emotion recognition in a clinical population with emotion processing deficits: Autism. The experimental design for our second study, and the results for our male and female participants will be reported and discussed in this chapter. The results for our autistic participants will be reported and reviewed in the next chapter.

5.1.1. PART A. CROSS-MODAL EMOTION RECOGNITION IN MALES AND FEMALES

A natural extension of our first study involves a shift from a unimodal visual task to a multimodal or cross-modal auditory-visual task within the two groups studied. In a number of recent studies, researchers have sought methods that would heighten the emotional message or content of their stimuli. For example, studies have employed facial emotion stimuli with exaggerated facial features, like 150% disgust. While these stimuli seem to have triggered a stronger, more visceral response in participants (Phillips et al., 1997), they are unnatural in appearance and may not reflect more natural emotion processing functions. Other studies have used silent films to elicit certain emotional responses but have been limited in the extent to

which they have controlled for consistencies in the facial emotions or social interactions portrayed across films (Lane et al., 1997). We have observed that at an elementary level, the recognition of visual facial identity is accomplished within unimodal processing areas, and that when processing requirements increase with tasks that require the assignment of emotional significance to stimuli, then broader multimodal or limbic circuits are engaged.

It may be suggested that by presenting information along two sensory channels we will create increased processing demands in these multimodal regions and therefore, provide a stronger method of exploring the process of emotion recognition. In fact, this suggestion has been illustrated in recent functional imaging studies of cross-modal tasks, where bimodal processing resulted in an amplification of the neuronal response seen in unimodal cortices (see Klingberg and Roland, 1998; Calvert et al., 1999). The present study, therefore, employed a cross-modal task in which participants are asked to match the auditory presentation of a series of proper names (James, John, etc.) that have been spoken with a particular emotional prosody with images of facial emotion. To our knowledge, functional activation studies of cross-modal emotion recognition are absent in the literature. In addition, functional imaging methods have only recently been applied in autism research and of the few studies that have been conducted only one has examined the processing of visual facial emotion (Critchley et al., 2000).

Hypothesis:

Drawing from the results of our first study, the requirements for visual facial emotion processing that make up part of the cross-modal task in this study, are expected to result in bilateral activation of the inferior frontal regions for female participants and a more strongly lateralized activation of the inferior frontal region for male participants. Given the multi-modal nature of the task, we may also expect to identify additional activation in the functional network of areas including the middle and superior temporal regions, amygdala and cingulate gyrus. Again, it is expected that the pattern of activation for females will be more distributed and less lateralized than that observed for male participants.

5.1.2. EXPERIMENTAL DESIGN

5.1.2.1. PARTICIPANTS

Three groups of young adults participated as participants in our second study: a group of Autistic males (n=8), a group of normal males (n=8) and a group of normal females (n=8). All of the participants were right handed, and they ranged in age from 20 to 33 years. The normal males were matched to the autistic group according to chronological age, sex, Non-Verbal IQ and handedness (see Chapter 6). The normal male and female participants were recruited by flyers posted on billboards across the university campus. They did not endorse drug or alcohol abuse, neurological or psychiatric disorders, a history of head injury, exposure to sources of radiation in the last year, or, a familial history of Autism. The female participants were screened for pregnancy, and all female participants were tested within the first 10 days of the start of their menstrual cycle. Ethics approval for the study was obtained from the McMaster University Ethics Committee. Informed consent was obtained from all participants prior to the study (See Appendix A). Most participants were scheduled for study in the afternoon.

5.1.2.2. THE ACTIVATION TASKS

There were two cross-modal experimental tasks utilized in this study. The first asked the participant to choose which of two faces (depicted to the right or left in a computer display) portrayed the same emotion as that heard in a voice with spoken with emotional content. The baseline task employed the same face stimuli as the emotion recognition task but asked participants to match the gender of the speaker (male or female voices spoken with neutral prosody) to the location of a male or female face (left or right).

Figure 22. Examples of Visual Stimuli used for
Gender Recognition and Emotion Recognition Trials
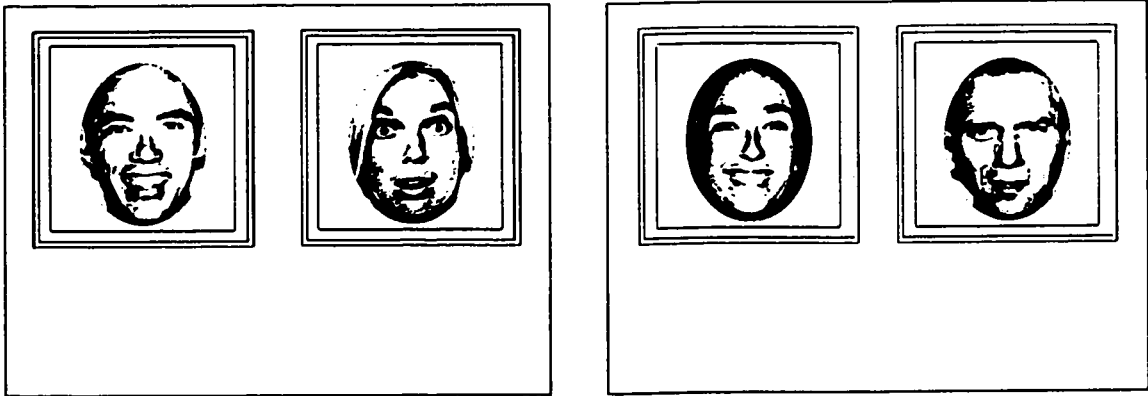
Examples of Gender matching stimuli
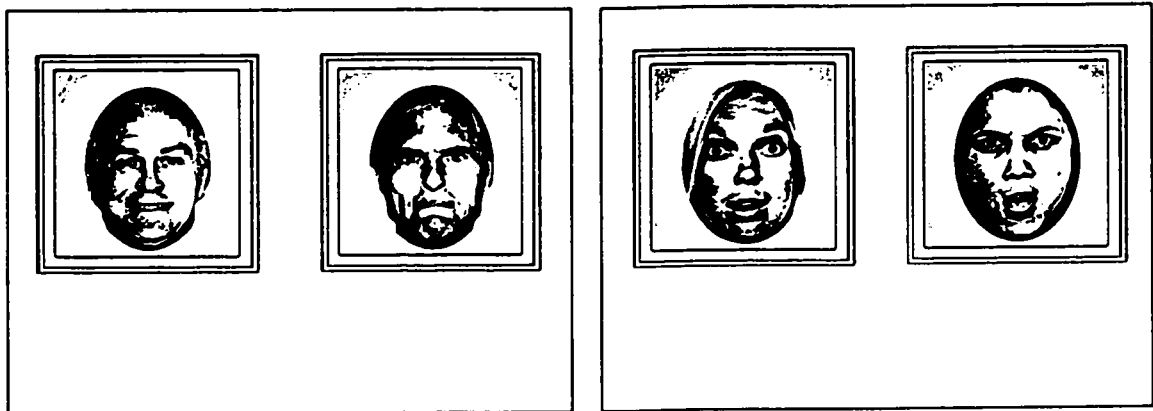
Examples of Emotion matching stimuli

The study utilized Ekman's standardized battery of faces (Ekman and Friesen, 1975) and

Sainsbury's images (Department of Psychology, University of Calgary) converted to image

format for the computer. Each face was bound by a frame and masked by an oval, so as to

present just the face.

Four emotions were selected to vary along 2 dimensions; intensity and valence (Heller, 1993):

positive valence / low intensity = happiness

positive valence / high intensity = surprise

negative valence / low intensity = sadness

negative valence / high intensity = anger

Actors voices (3 male, 3 female) were recorded speaking the proper names "John", "James", "Jason", "Jeremy", "Jeffrey" and "Joseph" with both neutral and emotional intonations matching the emotions above. The recordings were then converted into .WAV files for presentation by the computer. Each recording was edited to ensure consistent quality and to equalize the volume across all of the emotions. Each .WAV file was 1 second in duration, with the presentation of the voice beginning at 200 ms into the recording.

The emotional voice recordings were judged by 4 people using a 3 point rating scale: poor / fair / good (1, 2, 3) for the emotion they portrayed. A mean group score was calculated for each voice sample and only samples with a mean score of 2 or above were used in the emotion task construction. The neutral voices were used in the construction of gender recognition trials.

Two computer programs were written, each presenting eight blocks of matching trials (Appendix C; MEL; Psychology Software Tools, Pittsburgh, PA); one program started with the presentation of a gender matching block first, followed by emotion matching block, while the second program began with the emotion matching block first. Effort was made to balance the number of participants in each group receiving the two block orders.

Each block of emotion recognition trials was balanced for the number stimuli presented

for each emotion, the number of male / female stimuli, the number of correct answers

appearing in the left or right positions and the number of male / female faces appearing in the

incorrect choice or distracter position. Similarly, the gender recognition trials were balanced

for the number of male and female stimuli, the number of male / female faces appearing in the

correct choice position, and the number of male / female faces in the incorrect choice or

distracter position. Based on our experience during of Study I, the intertrial delay was reduced

600 ms by reducing the length of time the fixation point was visible, and the length of time

permitted for a response was shortened by 600 msec. A new stimulus was presented every 3.8

seconds for 96 trials.

Regional cerebral blood flow was mapped while participants performed the cross-modal

processing tasks (the $H_2^{15}O$ PET procedure used in this study is outlined in Chapter 3).

Visual stimuli were displayed on a video screen at a viewing distance of 40 to 50 centimetres.

The timing of the start of a block of trials presentation was concurrent with the injection of

$H_2^{15}O$ and the beginning of the second 30 second scan frame. Participants were asked to

indicate which of the two choice stimuli matched the auditory stimulus by pressing hand held

buttons with their right or left thumbs. Response latency and accuracy data were collected on

each trial.

5.1.3. RESULTS

All of the participants were right handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971) with right laterality quotients ranging from +63 to +100 on this measure. The normal male participants ranged in age from 20 to 30 years (mean = 23.5) and the normal females ranged in age from 21 to 23 years of age (mean = 22.7). Assessment with the Test of Nonverbal Intelligence (TONI: Proed), identified nonverbal IQS for the male participants that ranged from 90 to 135 (mean $\pm$sd = 109.4 $\pm$15.8). The female participants in this study had nonverbal IQS that ranged from 82 to 119 (mean $\pm$sd = 103.4 $\pm$14.4). There was no significant difference in nonverbal IQ between male and female participant groups, $t(14)$ = .793, p > 0.4.

5.1.3.1. PERFORMANCE DATA

Unfortunately, computer error resulted in a loss of response latency and error data for two male and three female participants. Response latency and error data for the remaining participants are summarized in Table 6.

The response latency and error data of participants for each task were analyzed using a repeated measures analysis of variance, with the within subjects factors identified as blocks and trials, and the between subjects factor identified as group (male or female). The results of these analyses are summarized in Appendix D. There were no significant differences between the error rates of male and female study groups to gender matching or emotion matching tasks (Table 6). In addition, there were no significant differences between the response latencies of male and female participants to the gender matching trials, nor any differences in response latencies between groups on emotion matching trials (Table 6).

Table 6.
Study II: Response Latency and Percent Correct for Gender Recognition and
Emotion Recognition, and Results of Group Comparisons using Repeated Measures ANOVAs

Task		Males Mean (sd)	Females Mean (sd)	Between Subject Effects F(1,9) p	
Gender	Latency	1250.3 ±316	1214.8 ±301	0.068	p> 0.80
	% Correct	98.3 ±2.6	98.8 ±1.0	0.379	p> 0.55
Emotion	Latency	1791.3 ±425	1793.9 ±428	0.000	p> 0.99
	% Correct	90.9 ±4.7	89.8 ±3.6	0.009	p> 0.93

The ANOVA within subjects factors blocks and trials showed significant effects for the

response latencies to gender recognition (blocks: $F(3, 27) = 3.624$, $p < 0.028$; trials: $F(35, 315)$

$= 3.790$, $p < 0.001$) and emotion recognition trials (blocks: $F(3,27) = 15.091$, $p < 0.001$; trials:

$F(35,315) = 4.835$, $p < 0.001$) . These findings identify that there were differences in the

latencies recorded for participants across the four blocks and across trials (Chart 3 and 4).

A significant block by group interaction was noted for both gender trials ($F(3, 27) = 3.214$,

$p < 0.042$) and emotion trials ($F(3, 27) = 11.409$, $p < 0.001$), identifying that the pattern of

response latencies for the male and female groups were different across the blocks.

A significant trial by group interaction was observed for the response latencies to emotion

recognition trials ($F(35, 315) = 1.543$, $p < 0.031$) identifying that males and females responded

differently across each of the trials.

The results from the Repeated measures ANOVAs on the errors to the gender

recognition task identified no significant within subjects effects across blocks or trials.

A significant effect was identified for the errors recorded across the blocks in the emotion

recognition trials (F(3, 27) = 11.650; p < 0.001). These findings identify that there are

differences in the errors recorded for the participants across the emotion task blocks. The

Charts 3, 4 and 6 demonstrate that the participants' response latencies and errors (for

emotion trials) generally decreased over the task blocks.

Chart 3. Study II: Male and Female Results:
Mean Response Latency of Gender Recognition
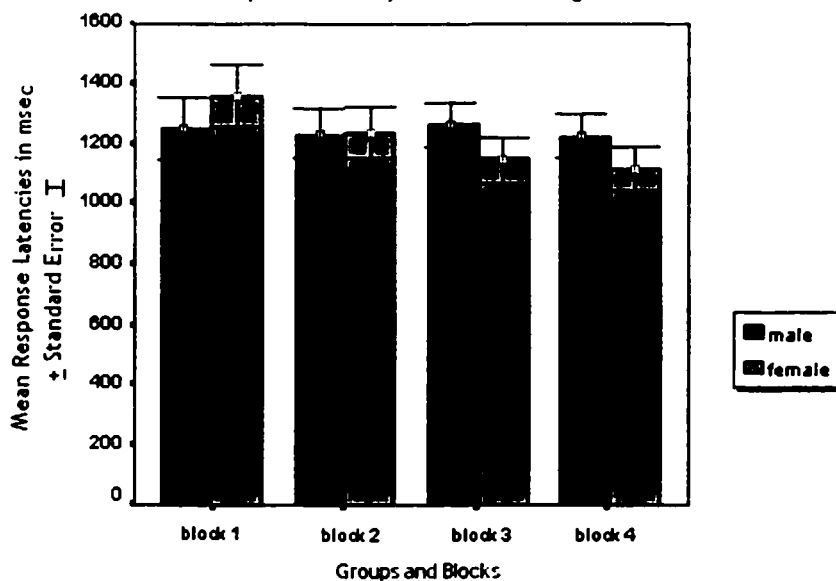
Chart 4. Study II: Male and Female Results:
Mean Response Latency of Emotion Recognition
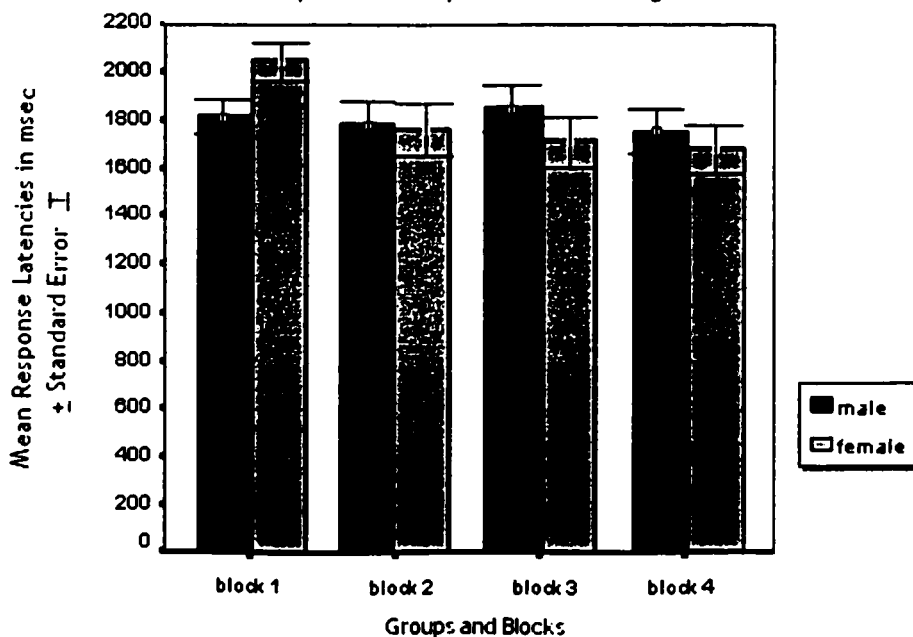
Chart 5. Study II: Male and Female Results:
Mean Percent Correct with Gender Recognition
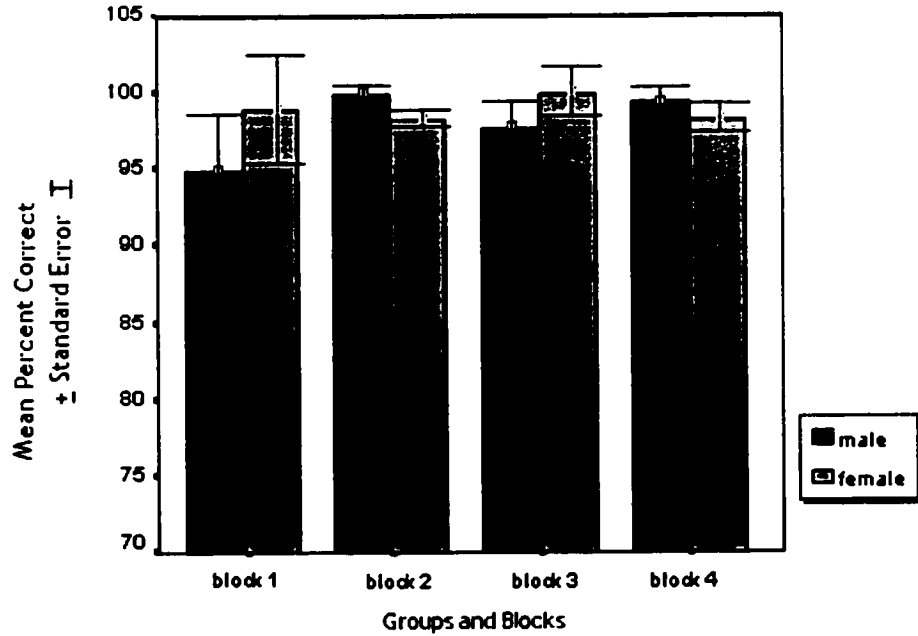
Chart 6. Study II: Male and Female Results:
Mean Percent Correct with Emotion Recognition
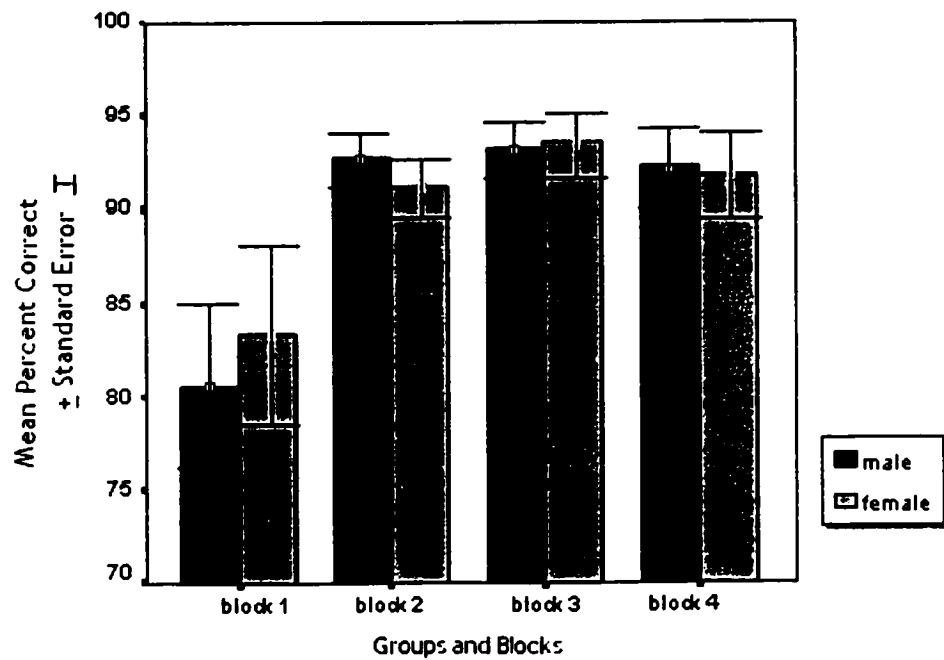
Table 7.
Comparison of Response Latency and Percentage Correct
for Emotion Recognition in Male and Female Study Groups

Emotion	Mean Response Latencies msec			Mean % Correct		
	Male mean ±sd	Female mean ±sd	Significance t(9) p	Male mean ±sd	Female mean ±sd	Significance t(9) p
Happy	1780 ±207	1752 ±177	0.16 p> 0.87	81 ±9.5	89 ±10.5	1.39 p> 0.19
Surprise	1767 ±240	1770 ±197	0.27 p> 0.97	92 ±5.8	94 ±3.8	0.51 p> 0.61
Sad	1846 ±233	1903 ±191	0.80 p> 0.43	95 ±5.8	88 ±4.1	2.31 p< 0.05
Angry	1707 ±212	1748 ±158	0.43 p> 0.67	93 ±7.7	93 ±6.5	0.17 p> 0.82

The response latencies of male and female participants were not significantly different across all four of the emotions presented (Table 7). With regard to the errors made for each emotion type, the male participants made significantly fewer errors to sad stimuli than the female participants. Error data for the other three emotion types did not distinguish between the male and female participant groups.

5.1.3.2. ACTIVATION DATA

The results from paired contrasts conducted with SPM '99 are presented below.

At this stage, within group analyses are presented in order to explore the strategies employed

by each group to perform the tasks. The t-test and p values are reported at the voxel level

and the illustrations display the result of comparisons conducted using a height thresholds of

0.001 and 0.01   (Figure 23).

Figure 23.   Key to Activation Images

■ Height Threshold set at p = 0.001

▨ Height Threshold set at p = 0.01
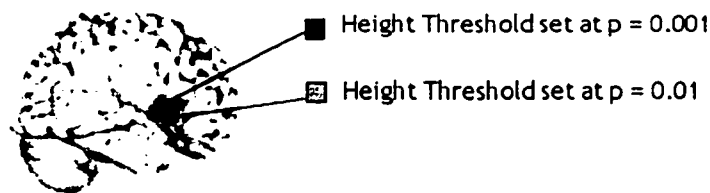
The two tasks employed in this study were quite similar. In both tasks, when

participants were presented with an auditory stimulus eg. "Jeffrey" they examined the two

face stimuli, and made a choice (right or left button push) according to the qualities of the

voice they heard. The emotion recognition task was distinguished from the gender recognition

task by the requirement that the voice and face stimuli were analyzed for their emotional

content. Contrasting the rCBF recorded during the cross modal emotion matching task with

that recorded for the gender matching task essentially identifies the neural activity specific to

the processing of emotional prosody and facial emotion.

5.1.3.3. CROSS-MODAL EMOTION RECOGNITION (EMOTION - GENDER)

The rCBF pattern produced when female participants performed emotion matching (contrasted with the baseline gender matching task) revealed activity located in the right superior temporal gyrus, right middle temporal gyrus, the left calcarine gyrus, the right middle occipital gyrus, the left superior occipital gyrus and the right anterior cingulate gyrus (Figure 24).

Figure 24. Female Participants Cross-modal Emotion Recognition :
Areas of significant increase in rCBF during Emotion Recognition trials as compared to Gender Recognition trials

left sagittal · right sagittal · medial sagittal

ventral transverse · dorsal transverse · posterior coronal · anterior coronal

1 right superior temporal gyrus	2 left calcarine gyrus
3 right middle occipital gyrus	4 right anterior cingulate gyrus
5 left superior occipital gyrus	6 right middle temporal gyrus
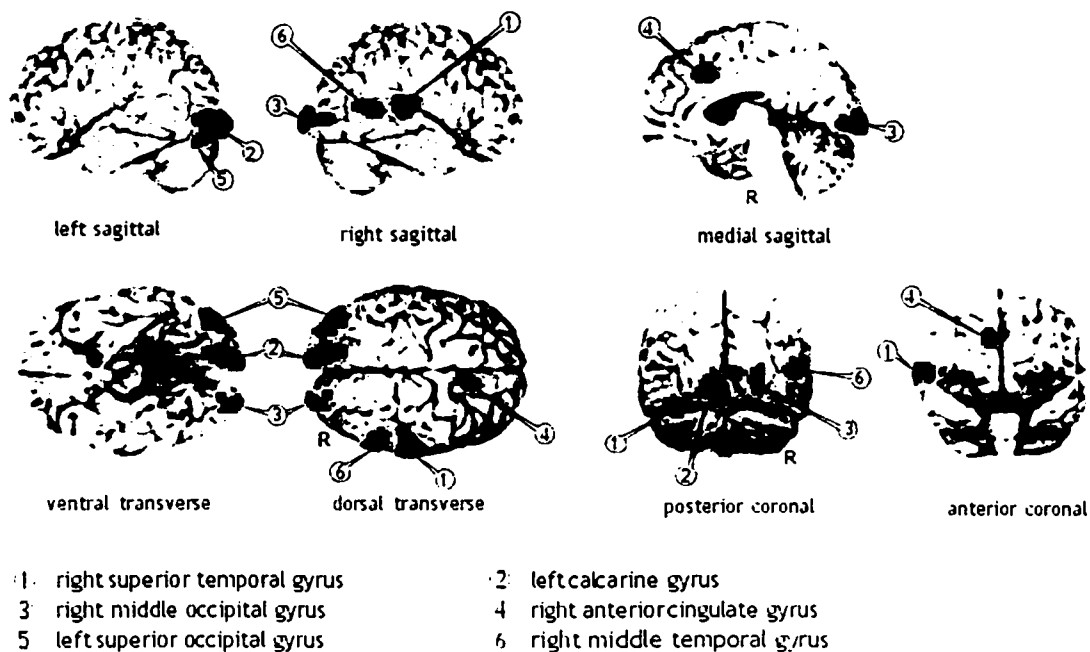
Contrasting the rCBF for emotion matching with that for gender matching trials for

male participants revealed activity in the temporal lobes bilaterally in the fusiform gyri, in the

left transverse temporal gyrus and the right inferior temporal gyrus (Figure 25). Frontal

activity was identified in the left inferior frontal gyrus, the left medial frontal gyrus and the

left precentral gyrus. Finally, activation was also identified in the right inferior parietal lobe.

Figure 25. Male Participants Cross-modal Emotion Recognition :
Areas of significant increase in rCBF during Emotion Recognition trials as compared to
Gender Recognition trials

| left sagittal | right sagittal |

| ventral transverse | dorsal transverse | posterior coronal | anterior coronal |

1 2	fusiform gyri	3	left inferior frontal gyrus
4	left medial frontal gyrus	5	left transverse temporal gyrus
6	right inferior parietal lobe	7	left precentral gyrus
8	right inferior temporal gyrus		
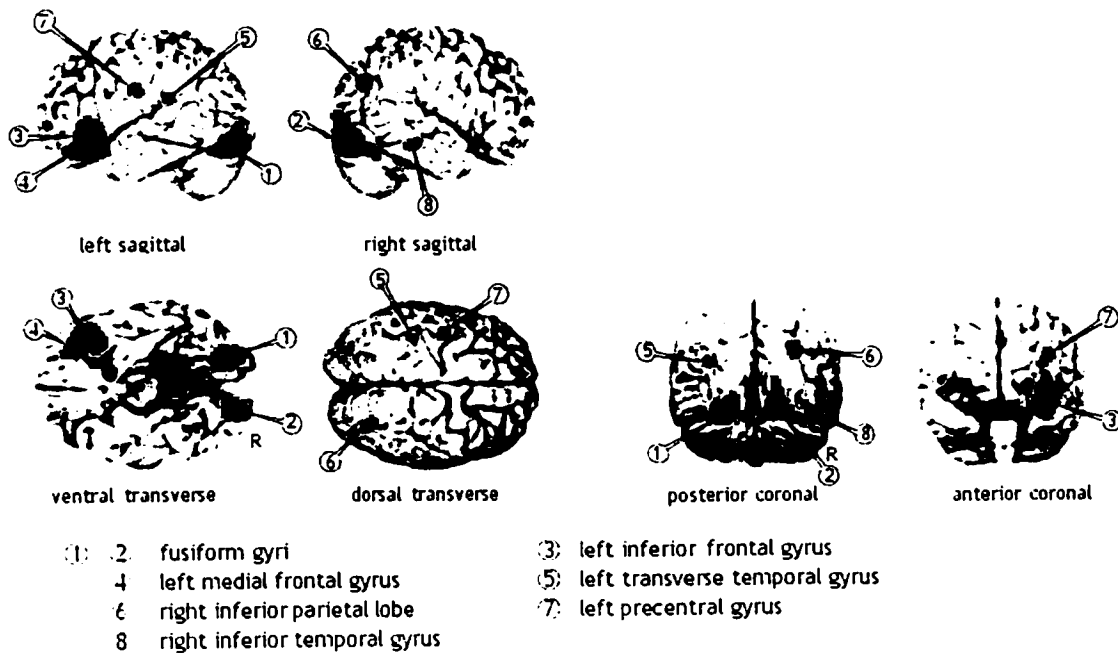
Figure 26. Within-Group Activation Patterns with Cross-Modal Emotion
Recognition in Male and Female Participants

■ Male

Female

Table 8. Regions of Significant Change in Regional Brain Activity Identified
through Contrasts of the Experimental Conditions

Group	Subtr action	Brain Location according to Talairach	Talairach x, y, z (mm)			Brod mann Area	t value	p value uncorrect ed
Female	E - G	R superior temporal gyrus	73	-16	12	22	4.21	p < 0.001
		L calcarine sulcus	-14	-81	1	17	4.06	p < 0.001
		R middle occipital gyrus	26	-98	7	18	3.45	p = 0.001
		R cingulate gyrus	10	25	34	32	3.25	p = 0.001
		L superior occipital gyrus	-38	-82	23	19	3.24	p = 0.001
		R middle temporal gyrus	57	-44	8	21	3.17	p = 0.001
Male	E - G	L fusiform gyrus	-22	-78	-11	18/19	4.80	p < 0.001
		R fusiform/lingual gyrs	22	-84	-9	19	4.01	p < 0.001
		L inferior frontal gyrs	-38	32	-12	47	3.97	p < 0.001
		L medial frontal gyrus	-30	39	-20	11	3.58	p < 0.001
		L transverse temporal g	-36	-28	21	41fls	3.36	p = 0.001
		R inferior parietal lobe	34	-63	31	39	3.22	p = 0.001
		L precentral gyrus/ middle frontal gyrus	-40	-3	26	4	3.16	p = 0.001
		R inferior temporal gyrus	46	-36	-15	20	3.08	p = 0.001

5.1.4. DISCUSSION

The response latency and error data for both study groups demonstrate that the emotion recognition task was more difficult than the gender recognition task. Both longer response latencies and greater errors were recorded for males and females during the emotion recognition trials. The male and female study groups performed both tasks quite similarly, with the exception that the female participants were somewhat faster in responding to the gender recognition trials than their male counterparts. An examination of the emotion recognition trials showed similar performances across the sexes. The two groups were only distinguished by fewer errors by males on sad emotion trials. These findings seem to conflict with the suggestion that females are better at emotion recognition than males, however ceiling effects could have attenuated any sex differences in error scores.

5.1.4.1. REGIONAL ACTIVATIONS
WITH CROSS-MODAL EMOTION RECOGNITION IN FEMALES

The areas activated by the cross-modal emotion recognition task (relative to the gender recognition task) in females included extensive regions in the occipital cortex, areas of the right temporal lobe and the right anterior cingulate gyrus. Previous functional imaging studies have demonstrated lateral occipital activation with emotion recognition (George et al., 1993; Nakamura et al., 1999; Phillips et al., 1997). Similarly, occipital activation was noted for the female participants in our first study during visual emotion recognition trials. It was suggested that this result could be attributed to either increased visual processing demands during emotion recognition trials or an effect of modulating feedback from the amygdala on visual association areas (Aggleton, 1993). Unfortunately, the present experiment cannot clarify which of these two possibilities is more likely. Response latency and error data indicate that the gender discrimination task was easier than the emotion recognition task.

The possibility remains that the emotion recognition task required more extensive processing of the visual stimulus. However, the identification of activation in the middle temporal cortex suggests that these areas were activated as part of the larger functional network concerned with emotion processing. As detailed in Chapter Four, a number of functional imaging studies have identified middle temporal cortex activation with emotion processing. In addition the MEG study of facial emotion processing by Streit et al. (1999) identified both middle temporal cortex and occipital activation during the processing of facial emotion. Finally, it may be suggested that this activation does not reflect new or additional neural systems engaged to support or coordinate the cross-modal performance. A recent study by Klingberg and Roland (1998) compared rCBF changes identified during auditory, visual, and cross-modal auditory-visual working memory tasks and found that *all* of the clusters of activation associated with the dual task performance overlapped with areas identified in single task activations.

Significant superior temporal activation was also identified when the female participants were engaged in the emotion recognition task (compared to gender recognition). This area corresponds to both the primary and association auditory cortices (Creutzfeldt, Ojemann and Lettich, 1989). However, the observation of this activation unilaterally suggests that it resulted from something more than the processing of the incoming auditory stimuli. Both the gender and emotion recognition tasks involved auditory stimuli of the same duration and volume and the increases in blood flow associated with the auditory processing demands of each task should have essentially cancelled each other out. The right superior temporal activation, then, more likely reflects the processing of the emotional prosody in the voice stimuli. This suggestion is made, given the special role assigned to the right superior temporal gyrus in the processing of emotional prosody by lesion studies. Aprosody deficits occur with

right hemispheric lesions (Heilman et al., 1984), however, the most severe deficits in aprosody

seem to occur with temporoparietal lesions, and in particular, lesions to the right posterior

Sylvian region (inclusive of the superior temporal gyrus) (Darby, 1983; Starkstein et al., 1994).

Moreover, right sided superior temporal activation has been reported in other studies of

emotion processing, including an imaging study that used facial stimuli conveying the emotion

disgust (Phillips et al., 1997), and an MEG study of facial emotion processing (Streit et al.,

1999).

Increased superior temporal activation seen with emotion recognition may also

reflect a heightened neural response associated with the cross-modal demands of the task.

This suggestion arises from recent research demonstrating that when multisensory inputs are

semantically congruous, they produce an amplification of the neural response in participating

sensory cortices (Calvert et al., 1999). In a study by Calvert et al. (1999) participants were

presented with a cross-modal task consisting of short film segments of someone speaking

the numbers one through ten. The unimodal tasks involved seeing the speaker without an

accompanying voice, or presentation of the voice with a static image of a face.

Voxel-by-voxel comparisons of fMRI activations in the auditory (BA 41/42) and visual cortices

revealed increased signal intensity during the cross-modal task, as compared to the unimodal

tasks. In a similar vein, signal amplification has been demonstrated in the lingual gyrus in a

cross-modal tactile/spatial visual attention paradigm investigated by Macaluso, Frith and

Driver (2000). It has been suggested that cross-modal effect of accentuating the neural

response in unimodal regions is the result of back-projections from multimodal regions

(Macaluso, Frith and Driver, 2000). Coupled with the localization of functions associated with

the processing of emotion in the right hemisphere, it is possible that feedback projections

from multimodal regions, including the amygdala, heightened the neural response in the auditory cortices of our female participants. Our research findings, then, of activation in right superior temporal association cortex may reflect multimodal feedback associated with processing of emotional prosody.

The final area of significant activation in the female emotion recognition data was the anterior cingulate gyrus. The cingulate gyrus is a component of the limbic system and receives efferent from the amygdala along the amygdalofugal pathways. Activity in the anterior cingulate has been identified in previous studies that have examined the neural responses to emotional expressions and emotional stimuli (George et al., 1993; Lane et al., 1998; Blair et al., 1999 ; Morris et al., 1996). It has been suggested that the anterior cingulate plays a role in the conscious experience of emotion (Lane et al., 1998). Another plausible explanation of cingulate gyrus activation is suggested by the participation of this region in attention processes. Extensive projections link the cingulate with the dorsolateral frontal lobe and the inferior parietal lobe (Heilman et al., 1984) and the anterior cingulate is thought to play a role in attention to stimuli when the selection of a response is required (Posner, 1994). Within the context of the present study, the involvement of the anterior cingulate in either the experience of emotion or attentive processes engaged in response selection appear equally plausible, and therefore cannot be resolved at this time.

In light of the findings from our first study, it is notable that we did not observe inferior frontal activation for the female participants. One interpretation may be that the processing of emotion in faces may be a relatively automatic process and therefore the use of the same set of visual stimuli for both the gender recognition and the emotion recognition

trials in our second study led our female participants to process the emotional content of the visual stimuli across in all trials. The subtraction of the activation for gender trials from that of the emotion trials could have removed this frontal activation.

5.1.4.2. REGIONAL ACTIVATIONS WITH CROSS-MODAL EMOTION RECOGNITION IN MALES

The observation of bilateral fusiform activation during emotion recognition is consistent with the body of functional imaging research demonstrating increased neural activity in this area with the visual presentation of face stimuli and facial identity recognition tasks. It may be suggested that visual gender discrimination may be achieved more holistically, and may not require the processing of the more detailed features of faces. In this regard, the study by Sergent, Ohta and Macdonald (1992) demonstrated that visual gender recognition, as compared to the discrimination of sine wave gratings, activated the ventral occipito-temporal cortex. In addition, when the recognition of facial identity (famous faces) was contrasted with gender recognition, the right lingual and fusiform regions were engaged, as well as the left middle temporal gyrus and both anterior temporal poles. The activation observed in the right inferior parietal lobe of our males may also reflect increased attention and spatial processing with cross-modal emotion matching as compared to gender matching. Furthermore, the activation of the left transverse temporal gyrus in these participants may reflect the demand for increased processing of the auditory stimuli when the extraction of the prosodic qualities of the voices was required as compared to the processing necessary in discrimination of gender (largely pitch). These findings identify that the processes involved in the cross-modal matching of emotion engage different or additional neural networks that distinguish these processes from those responsible for cross-modal gender recognition. This suggestion is further supported by the observation that gender

recognition can be spared in patients with lesions that produce disabilities in identity

recognition (prosopagnosia) (Tranel, Damasio and Damasio, 1988).

A relatively large local activation associated with cross-modal processing of emotion

was observed in the left inferior frontal cortex of our male participants. In their study of

visual emotion recognition, George et al. (1993) reported bilateral activation of inferior

frontal cortex when the rCBF identified for participants during facial emotion recognition trials

was contrasted with that recorded during identity recognition trials. They noted greater left

over right frontal activation and concluded that the left frontal and prefrontal cortex plays an

integral role in systems that regulate emotion and recognize the emotional content of sensory

input. Nakamura et al. (1999) similarly reported bilateral frontal activation with emotion

recognition as compared to a baseline color discrimination task, but here, the right inferior

frontal cortex demonstrated a larger response. In addition, when the activation associated

with emotion recognition was contrasted with another task in which facial processing was

required, (judgements of facial attractiveness), only the right side inferior frontal activation

remained (Nakamura et al., 1999). The results of our first study using similar visual stimuli to

Nakamura et al.'s (1999) study, certainly suggest that for females both the right and left

frontal lobes participate in emotion recognition. In addition, our findings suggest that the

responses of males to emotional stimuli tend to be more highly lateralized than those of

females. The left sided activation of the inferior frontal cortices in our male participants,

however, does contrast with the right sided activation observed for the males in our first

study, and the right frontal results in the male participants of Nakamura et al. (1999).

However, the observations in the latter two studies relate solely to the processing of visual

stimuli, and consideration should be given to the auditory demands of our task.

A recent fMRI study has investigated emotional prosody by presenting recordings of single words spoken with emotional intonation (happy sad angry and neutral) and varying the task demands such that participants needed to listen for a target word or a target emotion (Buchanan et al., 2000). A contrast of the activation identified during the emotion task with that of the word detection task revealed significant activation in the right inferior frontal lobe, the left cingulate gyrus and right inferior parietal lobe. The reverse contrast identified significant increases in neural activity during word detection in the left inferior frontal lobe, the left middle temporal gyrus and the right lingual gyrus and cuneus (Buchanan et al., 2000). These findings suggest that during the presentation of emotionally prosodic words, attention to the emotional content activates the right frontal region, while attention to the phonetic features of the words activates the left inferior frontal region. These findings converge with the results from functional studies of visual emotion recognition in identifying right inferior frontal activity with emotion processing. In the absence of previous functional research on cross-modal recognition, we might predict that our cross-modal task would result in significant activation of the right inferior frontal cortex. However, we have observed quite the opposite.

Exploring emotional prosody further, we find that lesion studies identify aprosody with either left or right hemispheric damage, however, predominantly more patients with aprosody present with right hemispheric lesions (Starkstein et al., 1994; Heilman et al., 1984). Hornak et al. (1996) have reported that patients with lesions to the orbitofrontal and ventral frontal cortex are impaired in the expression of emotion and in the comprehension of facial and vocal emotion. These observations are consistent with the functional research discussed thus far. Furthermore, Hornak et al. (1996) reported that their patients' lesions were localized to either right, left, or bilateral frontal cortices. Of interest was the observation

that visual emotion recognition skills were preserved in some individuals, and prosodic skills were preserved in others, indicating that the two processes are quite distributed in the frontal regions and that they involve separable neural systems. This observation is significant because it offers us an alternate way of interpreting the present results.

If we consider the processing of emotion to be a neurologically distributed process, and assign to the frontal lobes the function of evaluating the emotional content of experiences and guiding subsequent action, then, the design of our cross-modal task may have influenced the degree to which processing was carried out by either the left or right hemispheres. We presented our emotional face and voice stimuli in concert. On each emotion recognition trial, our participants were required to listen to the emotional quality of the voice and *then* identify which of two emotional faces matched the voice. Although we did not directly label the stimuli for our participants, the possibility remains that they labelled the voice stimulus in order to guide the selection of an appropriate visual face stimulus. One possible explanation of the left-sided frontal activation in our normal males, then, may lie in the use of response strategy that involved verbally labelling the emotions.

Another possible source of the left sided activation with cross-modal emotion processing is raised by the research on split brain patients. In some individuals with infractible epileptic seizures the corpus callosum is surgically cut to limit the spread of the abnormal electrical discharge to one hemisphere. In individuals in which the entire corpus callosum was cut, the processes of right and left hemispheres are essentially isolated from one and other. By presenting information to the right or left visual hemifields of these individuals, researchers have identified cognitive capacities that are lateralized to each hemisphere. The study of

"split brain" patients has shown that both hemispheres are capable of generating spontaneous expressions of facial emotion, whereas, only the left hemisphere can generate voluntary facial expressions (Gazanniga and Smylie, 1990). With this in mind, it may be suggested that the activation of the left hemisphere in our male participants resulted because they mimicked the visual facial stimuli (at least subconsciously) as part of their approach to the task. The local activation identified along the more ventral aspect of the left precentral gyrus in our males appears to correspond to facial motor regions functionally defined by cortical mapping studies (eg. Lotze et al., 2000). It is possible that our male participants did not overtly copy the facial emotion stimuli, but imagined, or referenced the motor actions needed to produce the facial emotion depicted. This is suggested in view of the fact that activation of the primary motor cortex and premotor cortex has been identified when individuals both imagine performing and execute motor actions (Porro et al., 1996; Lotze et al., 1999).

One final account of the left sided activation with cross-modal processing in males stems from Gazzaniga's (2000) suggestion that the left hemisphere possesses the unique capacity to interpret, elaborate and make inferences about observed behaviors and emotional states. Under experimental conditions where the left and right visual hemifields are presented with different images, each portraying a different concept, and where there is a subsequent presentation of a series of objects that can be associated with either conceptual category, the split brain patient will select objects with his left hand that are linked to the conceptual category held by the right hemisphere, and objects with his right hand that can be associated with the concept held in left hemisphere. When questioned about the rationale for both choices, the split brain patient will try and interpret his responses so that they are consistent with the information held by the left hemisphere. Gazzaniga (2000) has suggested

that this tendency to generate explanations and hypotheses is carried out by a left hemisphere interpreter function which is wholly responsible for the construction of an integrated conscious experience. The interpreter is active in emotional experience too, and is seen in the split brain patient when a mood shift triggered in the disconnected right hemisphere results in attempts by left hemisphere to interpret the current experience. It may be suggested that the left sided activation with the cross-modal processing of emotion by our males, is consistent with Gazzaniga's idea that the left hemisphere is uniquely involved in drawing together an integrated conscious experience.

5.1.4.3. COMPARING THE ACTIVATIONS FOR FEMALES AND MALES

The PET rCBF results for the cross-modal matching of emotion revealed bilateral activation of the occipital region in females, and the fusiform region in males. It was suggested above that activation of these regions resulted from greater demands for the analysis of visual facial information and was reflective of multimodal feedback during affect matching as compared to gender matching. The activation patterns for our male and female participants, then, differed primarily with the identification of left inferior frontal activation for males, and right superior temporal and right anterior cingulate activation for females. A role for each of these regions in the processing of emotion has been established in previous functional imaging studies (George et al., 1996a; Buchanan et al., 2000; Morris et al., 1996; Blair et al., 1999; Phillips et al., 1997).

Placing the bilateral occipital / fusiform activations aside, our male and female results are distinguished from one and other by the hemisphere in which activations were found.

Theories that hold that the regional activity associated with an emotional experience can be localized in accordance with the particular valence and arousal level of the emotion, place the experience of pleasant emotions in the left hemisphere and unpleasant emotions in the right hemisphere, and, emotions low in arousal in the frontal regions and high in arousal within the parieto-temporal regions (Heller, 1993). The left frontal activation in our male participants, might be taken to reflect a pleasant , calm and happy reaction to the stimuli, whereas, the right temporal activation in our female participants might reflect a negative, anxious or angry reaction to stimuli. However, in this study, we have not attempted to draw out differences in the reaction of our participants to various emotions. The face and voice stimuli were not selected to evoke a particular emotion, but rather to examine the functional locations responsible for the extraction and processing of emotional information.

It is important to note that particular care was observed in the design of this study, so that a balance was struck between the valence and intensity of the four emotions conveyed. Furthermore, while the autonomic reactions of males and females to emotionally evocative films have been distinguished from one and other, these differences do not resemble the lateralized activations identified in the current study. Kring and Gordon (1998) demonstrated that males exhibit a greater galvanic skin response to films designed to elicit fear and anger, whereas females react more to films that generate feelings of sadness and disgust; no difference, however, was identified in the autonomic responses of males and females to films designed to elicit positive feelings (happiness) (Kring and Gordon, 1998). As such, the idea that our male and female participants reacted differently to both positive and negative emotional stimuli is not consistent with the results of Kring and Gordon which suggest that sex differences exist in emotional reactivity for negatively valanced emotionally provocative stimuli. Instead, it is suggested that our activation data reflect sex differences in the

functional organization of regions that participate in the processing of cross-modal displays of emotion.

It has been theorized for some time, that the functional asymmetry of the brain is more marked in males than in females (McGlone, 1980; Shaywitz et al., 1995). There is evidence from studies of lesion patients and the neuropsychological testing of normal adults that has suggested that, in the majority of cases, men have greater hemispheric specialization for verbal and non-verbal abilities whereas women are more likely to have bilateral representation of function (McGlone, 1980; Kimura and Harshman, 1984).

Evidence of sex differences in the morphometry of cerebral structures have been identified in midsagittal measures of the corpus callosum (Witelson, 1989; Clarke and Zaidel, 1994; Davatzikos and Resnick, 1998), the sylvian fissure (Witelson and Kigar, 1992) and in hemispheric grey matter volumes (Gur et al., 1999). Posterior callosal (isthmus/splenium) volumes that are larger for women than men have been identified at autopsy (Witelson, 1989) and in measures of midsagittal MRIs (Clarke and Zaidel, 1994; Davatzikos and Resnick, 1998). Callosal size has been positively correlated with performance on neuropsychological tasks that require bilateral processing, (Clarke and Zaidel, 1994), particularly for women (Davatzikos and Resnick, 1998). These findings have been interpreted as evidence of greater interhemispheric connectivity in women (Davatzikos and Resnick, 1998). The size of the posterior corpus callosum is largely determined by the number of small caliber fibers that are believed to connect homologous association cortices in the parietal and temporal regions of the two hemispheres (Aboitiz et al., 1992).

The relative connectivity between the two hemispheres may also factor in the observation of sex differences in measures of the Sylvian fissure. Witelson and Kigar (1992) examined the brains of 67 men and women obtained at autopsy and found that the horizontal segment of the posterior part of the sylvian fissure was longer in the left hemisphere than in the right. Furthermore, measurements of this region in the left hemispheres of men were significantly longer than those on the left for women. No sex difference was identified for similar measures of the right sylvian fissure. These findings may relate to the distribution of language and some spatial functions in the hemispheres and signify greater functional asymmetry in men and greater interhemispheric connectivity women (Witelson and Kigar, 1992).

The superior temporal gyri occupy the lower boundary of the posterior part of the sylvian fissure, and in the left hemisphere, in most individuals, this area is concerned with the comprehension of spoken language. The right superior temporal sulcus has been associated with the extraction of the prosodic qualities of voices (Darby, 1983; Kolb and Wishaw, 1990). Our identification of right superior temporal activation in women, but not men, may be a function of the greater interhemispheric connectivity of this region suggested for women. The largest localized activations were identified in the left frontal region for the males and in both the frontal (cingulate) and superior temporal regions for females. It may be suggested that these findings are consistent with the results of our first study which identified that processing of emotional stimuli is more distributed in females than males. This suggestion is further substantiated by fMRI evidence of bilateral activation of frontal cortices for women during the performance of phonological (rhyming) language tasks, as opposed to unilateral left hemisphere activation for males (Shaywitz et al., 1995).

One final distinction that can be drawn between the male and female patterns of activation concerns the relative emphasis the two sexes placed on the processing of the auditory and visual information in the stimuli. The observation of inferior frontal activation with cross-modal emotion matching in males parallels the activation reported in studies of visual facial emotion (e.g. Study I; George et al., 1993). This similarity suggests that cross-modal emotion matching in males is achieved largely by higher-order frontal processes that are responsible for integrating the whole emotional experience. Activation of the superior temporal gyrus in female participants was discussed above in relation to the processing of emotional prosody, and may indicate that females placed greater processing emphasis on the auditory qualities of the cross-modal emotion stimuli. These suggestions appear to be consistent with the more general notions regarding sex differences in behavior that hold that females possess relatively stronger verbal skills, while males tend to excel in visual/spatial areas.

5.1.5. CONCLUSION

To identify the neural substrates of cross-modal emotion recognition we studied eight male and eight female young adults with $H_2^{15}O$ PET. To our knowledge, functional studies of cross-modal emotion processing are absent in the literature. The cross-modal task used in this study required that participants match an auditorily presented prosodic target stimulus to one of two visual facial emotion stimuli, while the gender recognition task (baseline condition) required that they match male or female prosodically neutral voices with male or female facial stimuli.

The cross-modal matching of emotion, as compared to gender matching, resulted in significant bilateral activation of the occipital cortices in females and bilateral activation of the inferior temporal regions in males. It was suggested that in comparison to cross-modal gender recognition, the cross-modal matching of emotion requires greater visual analysis or the extraction of more detail from facial stimuli for both men and women. Additional regions of significant activation with cross-modal matching of emotion were identified in the left inferior frontal cortex for males, and in the right anterior cingulate gyrus and right superior temporal gyrus for females. These results were considered to be consistent with the view that cognitive processes show a greater functional distribution in females. These findings may also suggest that cross-modal processing by males is achieved more through integrative processes necessary for response selection, whereas females place greater processing emphasis on the prosodic qualities of the auditory target stimulus.

CHAPTER SIX

6.1 STUDY II:
PART B. CROSS-MODAL EMOTION RECOGNITION IN AUTISM

The results from functional imaging studies suggest that the neuropathology of autism is likely

the result of a disruption of a distributed network of functional regions that include the

amygdala, frontal lobes, cingulate gyrus, thalamus and visual association cortices.

An absence of normal connectivity is suggested by the identification of activation patterns for

individuals with autism that are less extensive (Baron-Cohen et al., 2000), or located in regions

lying adjacent to those activated by normal controls (Schultz et al., 2000; Happe et al., 1996).

Furthermore, a failure to engage this functional network, may lead to the adoption of different

response strategies and the recruitment of different neural systems. For example,

Baron-Cohen and associates (2000) hypothesized that their participants with autism had

performed theory-of-mind tasks without engaging the amygdala, and had instead engaged the

superior temporal regions as a result of a response strategy that emphasized verbal labelling.

Hypothesis: It is suggested that our participants with autism will be distinguished from

controls by a failure to activate the inferior frontal, amygdala and middle/superior temporal

regions during cross-modal emotion processing. It is also suggested that activation may be

identified in regions that reflect the use of compensatory or alternate processing strategies to

respond to the emotion processing task.

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6.1.1. EXPERIMENTAL DESIGN

For comparison purposes, the data reported in Chapter Five for our normal male subjects are repeated here. Eight young adults with autism and eight normal males participated in this second study. The participants ranged in age from 20 to 33 years. The normal males served as controls for the group with autism and were group matched according to chronological age, sex, Non-Verbal IQ and handedness (see results 6.1.2). The normal male participants did not endorse drug or alcohol abuse, neurological or psychiatric disorders, a history of head injury, exposure to sources of radiation in the last year or a familial history of autism. The participants with autism carried a medical (DSM; APA, 1994) diagnosis of autism or Pervasive Developmental Disorder (PDD), and they (and/or their parent/guardian) did not endorse any comorbid neurological or psychiatric disorders such as tuberous sclerosis, or Tourettes Syndrome, drug or alcohol abuse, a history of head injury, seizures or exposure to radiation in the last year.

The normal male participants were initially recruited from a local millwright apprenticeship program. It was thought that individuals registered in this program would probably have good visual spatial skills, and perhaps, be less adept verbally, and therefore make good controls for the group with autism. However, successive cancellations and no-shows prompted a shift to the use of volunteers recruited by flyers posted on billboards across the university campus. The participants with autism were recruited from a support group offered to adults with autism by the Geneva Centre for Autism in Toronto, and from a local preparation-for-independent-living program: the Woodview Manor in Hamilton. Some of the participants in the latter setting have been willing and able participants in a previous study (see Wainwright and Bryson, 1996). Pamphlets and a parent letter were developed to assist in the

recruitment of participants with autism (Appendix B). In addition, an orientation film depicting the scan procedure was shown to most of the participants with autism to improve their understanding of the study. The film also helped to prepare the participants and allay any fears they might have, reducing the likelihood that they would become overly anxious during the scan procedure.

Most participants were scheduled for study in the afternoon. The Test of Nonverbal Intelligence (Proed) and the Edinburgh Handedness Inventory (Oldfield, 1971) were administered prior to the PET procedure and the participants were assured that the results from these tests would be kept strictly confidential and used only for matching purposes. In addition, head circumference was measured in the participants with autism and male controls. Potential participants were excluded from the study if they were left handed or obtained a non-verbal IQ below 69.

6.1.2. RESULTS

The normal male participants ranged in age from 20 to 30 years (mean = 23.5) and the participants with autism ranged in age from 20 to 33 years (mean = 27.6). There was no significant difference between the mean age of the male control group and the group with autism ($t(14) = 1.7$, $p > 0.1$). Assessment with the TONI (Proed), identified nonverbal IQS for the control male group that ranged from 90 to 135 (mean $\pm$sd = 109.4 $\pm$15.8). The nonverbal IQS of the participants with autism ranged from 80 to 130 (mean $\pm$sd = 105 $\pm$18.1). There was no difference in nonverbal IQ between the participants with autism and the control males ($t(14)$ = 0.46 $p > 0.7$). As a result, no participants were excluded from the study on the basis of the non-verbal IQ scores. On head circumference measures the participants with autism ranged

from 55.9 to 61.0 cm (mean ±sd = 59.2 ±2.06) and the normal males ranged from 57.2 to 61.0

cm (mean ±sd = 58.4 ±1.63). There was no difference between the mean measures of head

circumference for the participants with autism and the controls (t (14) = .76, p > .5).

6.1.2.1. PERFORMANCE DATA

Unfortunately, computer error resulted in the loss of response latency and error data

for one participant with autism and two male controls. The results for the remaining data sets

are reported here (Table 9). The response latency and error data of participants for each task

were analyzed using a repeated measures analysis of variance, with the within subjects factors

identified as blocks and trials, and the between subjects factor identified as group (control or

autism). The results of these analyses are summarized in Appendix D. There were no

differences between the response latencies of the two study groups to gender matching or

emotion matching tasks (Table 9). In addition, there were no differences between the error

rates of the participants with autism and the controls to the gender matching trials.

A significant difference, however, did emerge between the errors recorded for the participants

with autism and those identified for the controls during emotion matching trials (Table 9).

Table 9.

Study II: Response Latency and Percent Correct for Gender Recognition and Emotion
Recognition and, Results from Group Comparisons using Repeated Measures ANOVAs

Task		Control Mean (sd)	Autism Mean (sd)	Between Subject Effects F (1, 11)	p
Gender	Latency	1250.3 ±316	1347.1 ±488	0.428	0.529
	% Correct	98.3 ±2.6	91.7 ±8.1	2.708	0.131
Emotion	Latency	1791.3 ±425	1771.3 ±535	0.027	0.872
	% Correct	90.9 ±4.7	68.0 ±15.2	10.422	0.008

The ANOVA examining response latencies to gender recognition trials identified no

significant effect for the within subjects factor blocks and a significant effect for trials

$(F(35, 385) = 4.751, p < 0.001)$. These findings identify that the response latencies across the

gender blocks were not different, however there were differences recorded in the latencies

from gender trial to gender trial (Chart 7). Similarly, the ANOVA conducted on the response

latencies to emotion recognition trials showed no significant effect for blocks and a significant

effect across trials $(F(35, 385) = 3.451, p < 0.001)$. These findings identify that the response

latencies to emotion matching trials were not significantly different from block to block

(Chart 8), and yet differences existed in the latencies recorded for participants from one trial

to the next.

Chart 7.   Study II: Autism and Control Results:
Mean Response Latency of Gender Recognition
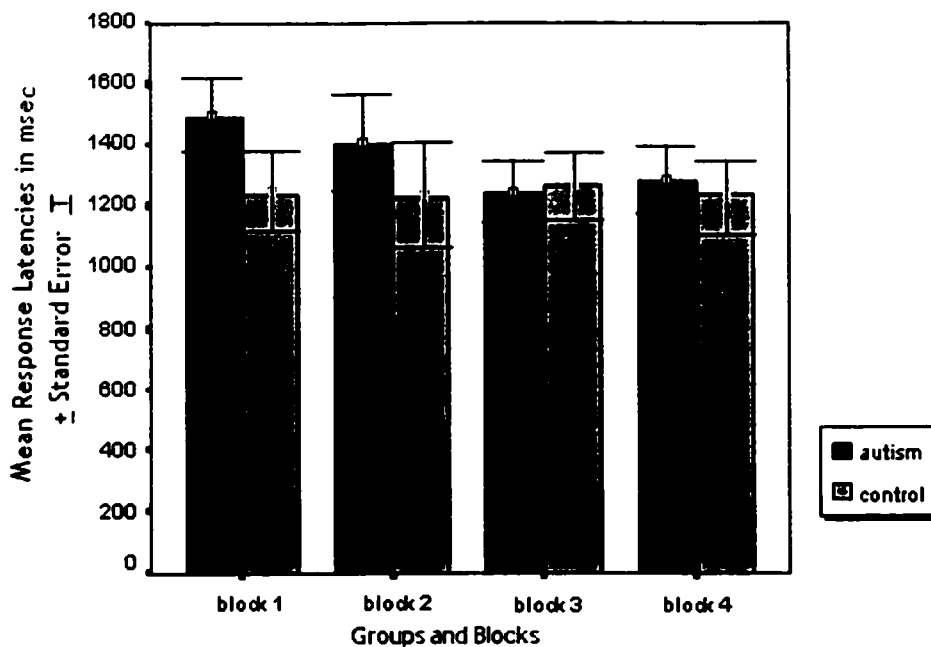
Chart 8.   Study II: Autism and Control Results:
Mean Response Latency of Emotion Recognition
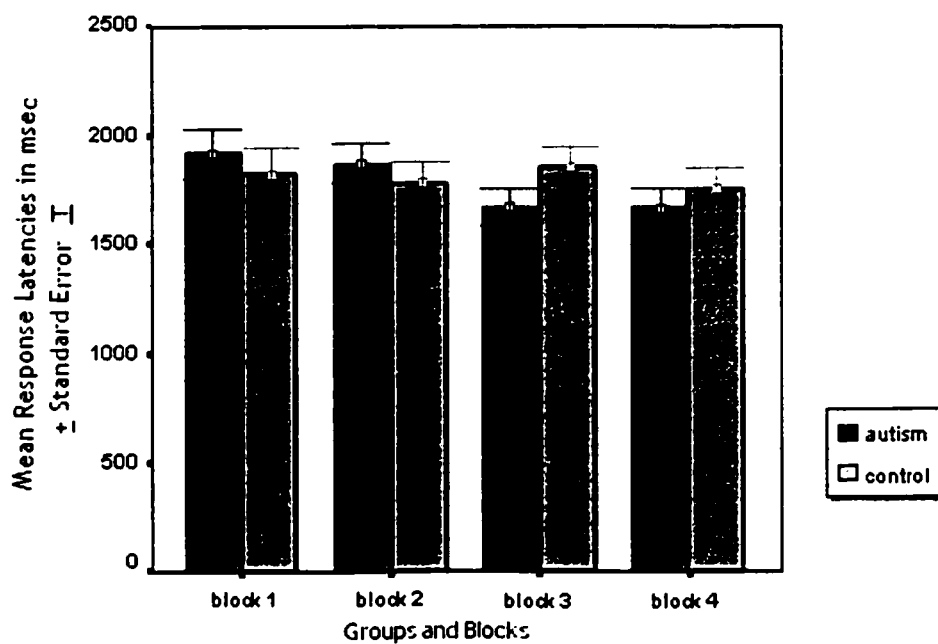
Chart 9. Study II: Autism and Control Results:

Mean Percent Correct with Gender Recognition
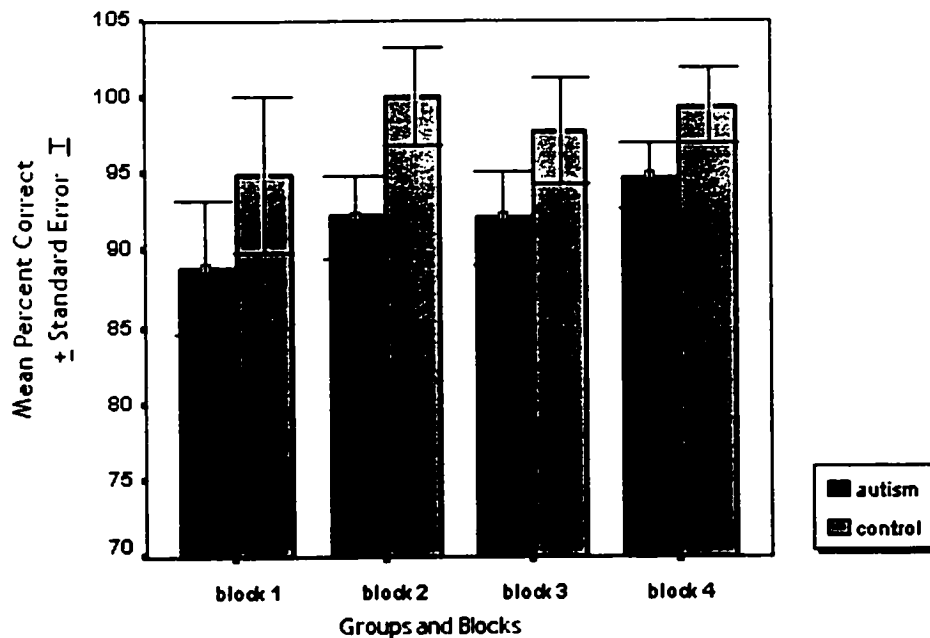
Chart 10. Study II: Autism and Control Results:

Mean Percent Correct with Emotion Recognition
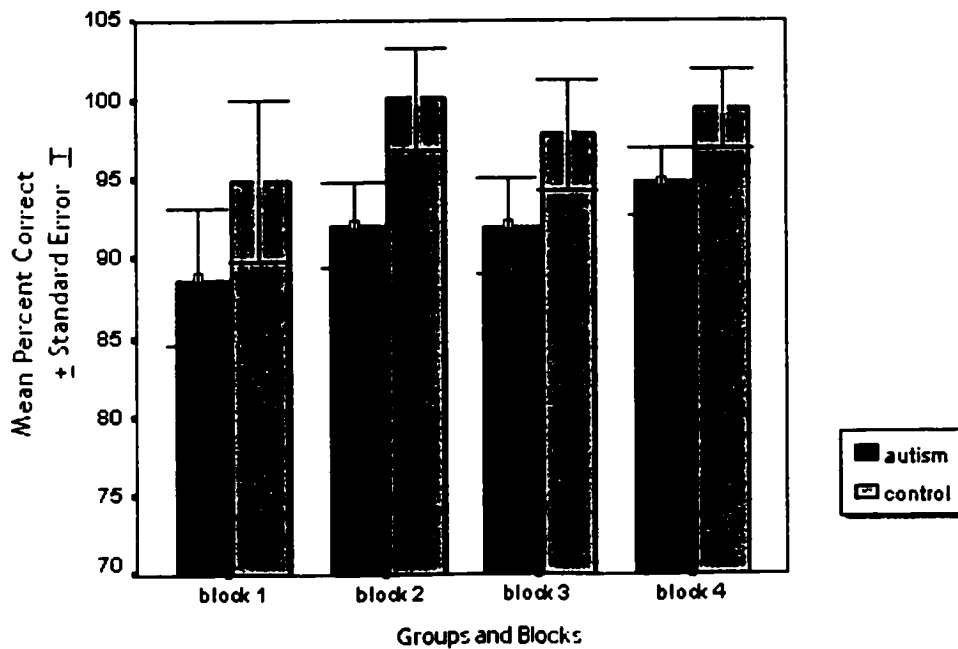
task identified no significant within subjects effects (Chart 9). The ANOVA conducted on the errors to emotion recognition trials identified a significant effect for blocks ($F(3, 33) = 6.729$, p. < 0.002) and a block by group interaction effect ($F(3, 33) = 2.984$, p < 0.046). These findings identify that there were differences in the errors recorded across the blocks, and that from block to block the errors identified for the controls and the adults with autism were different (Chart 10).

Paired t-tests conducted on the response latency data for the autism and control study groups, identified that both groups responded faster to the gender recognition trials than the emotion recognition trials (control $t(5)=8.17$, p < 0.001 ; autism $t(6)=6.61$, p < 0.002). Furthermore, both groups made more errors on the emotion recognition trials than on the gender recognition trials :control $t(5) = 3.01$ p < 0.04); autism ($t(6) = 6.86$, p < 0.001).

Examining the response latency and error data for each of the emotions presented in the emotion trials, we find that there are no differences between the response latencies for the participants with autism and controls on any of the emotions (see Table 10). The participants with autism, however, did make more errors than the controls on three of the four emotions; surprise, sadness and anger.

Table 10.
Analysis of Response Latencies and Errors
to the Emotion Recognition Stimuli for Autism and Control Groups

Emotion	Mean Response Latencies msec			Mean % Correct		
	Autism mean ±sd	Control mean ±sd	Significance $t(11)$ P	Autism mean ±sd	Control mean ±sd	Significance $t(11)$ p
Happy	1748 ±237	1780 ±207	0.15 p > 0.88	69 ±16.3	81 ±9.5	1.55 p > 0.14
Surprise	1758 ±217	1767 ±240	0.08 p > 0.93	72 ±15.2	92 ±5.8	2.99 p < 0.012
Sad	1890 ±165	1846 ±233	0.84 p > 0.41	58 ±24.8	95 ±5.8	3.62 p < 0.005
Angry	1655 ±275	1707 ±212	0.30 p > 0.76	69 ±26.3	93 ±7.7	2.19 p < 0.05

To examine the question of whether the type of emotion presented had an effect on the performance for the participants with autism, one-way repeated measures ANOVAs were conducted on their emotion task data. Significant within-subject effects were identified in the response latencies to each of the emotion stimulus types and in the errors committed ($F(3, 579)$ = 10.53, p< 0.001; F (3, 651) = 5.02, p < 0.003, respectively). Similar repeated measures ANOVAs were conducted on the response latency and error data for the controls, and significant within-subject effects were observed in this data too (latency: ($F(3, 534)$ = 4.76, p < 0.003; errors: F (3, 552) = 9.99 p < 0.001). These findings indicate that type of emotion had an effect on the latencies and errors of both groups of participants. In particular, the slowest mean latencies were identified in the responses of both groups to the sad stimuli. Furthermore, the controls demonstrated the lowest mean percent correct on happy emotion trials, whereas the participants with autism performed most poorly on sad emotion trials.

6.1.2.2. ACTIVATION DATA

Contrasting the rCBF for emotion matching with that for gender matching trials for controls revealed activity in the temporal lobes bilaterally in the fusiform gyri, in the left transverse temporal gyrus and the right inferior temporal gyrus. Frontal activity was identified in the left inferior frontal gyrus, the left medial frontal gyrus and the left precentral gyrus. Finally, activation was also identified in the right inferior parietal lobe.

Figure 27. Male Controls Cross-modal Emotion Recognition :
Areas of significant increase in rCBF during Emotion Recognition trials as compared to Gender Recognition trials

| left sagittal | right sagittal |

| ventral transverse | dorsal transverse | posterior coronal | anterior coronal |

	2	fusiform gyri		·3	left inferior frontal gyrus
	4	left medial frontal gyrus		5	left transverse temporal gyrus
	6	right inferior parietal lobe		7	left precentral gyrus
	8	right inferior temporal gyrus			

Note: this Figure is the same as Figure 25 on page 116.

Contrasting the rCBF for emotion matching with that for gender matching trials for participants with autism revealed activity bilaterally in the anterior temporal poles, in the left inferior frontal gyrus, the right cuneus, the left fusiform gyrus, and the right and left anterior cingulate / medial frontal gyrus.

Figure 28. Participants with Autism Cross-modal Emotion Recognition: Areas of significant increase in rCBF during Emotion Recognition trials as compared to Gender Recognition trials

left sagittal   right sagittal   medial sagittal

ventral transverse   dorsal transverse   posterior coronal   anterior coronal

(1) left inferior frontal gyrus   2) (7) anterior temporal poles
(3) anterior cingulate   (4) right cuneus
(5) right middle frontal gyrus   (6) left fusiform gyrus
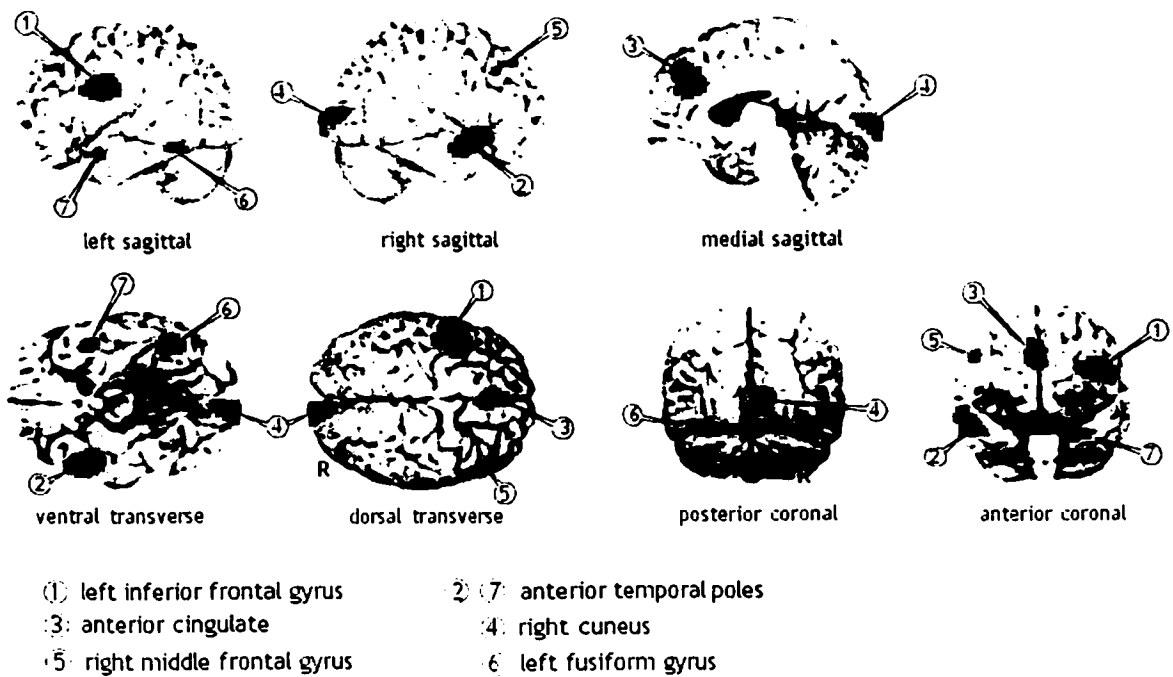
Figure 29. Within-Group Activation Patterns with Cross-Modal
Emotion Recognition in Controls and Participants with Autism

■ Autistic

■ Control

Table 11. Regions of Significant Change in Regional Brain Activity Identified
through Contrasts of the Experimental Conditions

Group	Subtr action	Brain Location according to Talairach	Talairach Coordinates x,y,z (mm)			BA	t value	p value uncorrected
Control	E - G	L fusiform gyrus	-22	-78	-11	18/19	4.80	p < 0.001
		R fusiform/lingual gyrs	22	84	-9	19	4.01	p < 0.001
		L inferior frontal gyrs	-38	32	-12	47	3.97	p < 0.001
		L medial frontal gyrus	-30	39	-20	11	3.58	p < 0.001
		L transverse temporal g	-36	-28	21	41fls	3.36	p = 0.001
		R inferior parietal lobe	34	-63	31	39	3.22	p = 0.001
		L middle frontal gyrus/ precentral gyrus	-40	-3	26	6	3.16	p = 0.001
		R inferior temporal gyrus	46	-36	-15	20	3.08	p = 0.001
Autism	E - G	L inferior frontal gyrus	-48	7	27	44	4.27	p < 0.001
		R temporal pole	51	11	-17	38	4.23	p < 0.001
		R/L ant cingulate/ medial frontal gyrus	0	42	31	9/32	3.57	p < 0.001
		R cuneus	10	-92	8	17	3.69	p < 0.001
		R middle frontal gyrus	48	39	35	9	3.37	p = 0.001
		L fusiform gyrus	-42	-47	-14	37	3.34	p = 0.001
		L temporal pole	-39	11	-21	38	3.25	p = 0.001

6.1.3. DISCUSSION

Consistent with results for male and female participants, the response latency and error data for our participants with autism indicates that the emotion recognition task was more difficult than the gender recognition task. The examination of response latency and error data collected during the gender recognition task showed that the group with autism performed as well as the controls. This was not the case for emotion recognition trials, where despite similar response latencies, the group with autism made significantly more errors than the controls. These findings are consistent with research identifying emotion recognition difficulties in autism (Capps, Yirmiya and Sigman, 1992; Hobson et al., 1988a;b). In previous autism research, cross-modal emotion recognition has been studied in mentally handicapped adolescents and adults with autism (Hobson et al., 1988a;b). The present results extend these findings and demonstrate cross-modal emotion recognition difficulties in high functioning adults with autism.

6.1.3.1. REGIONAL ACTIVATIONS WITH CROSS-MODAL EMOTION RECOGNITION IN ADULTS WITH AUTISM

Similar to the findings for our controls, the participants with autism engaged the fusiform gyrus during the cross-modal emotion recognition trials. Although the activation in our control group was bilateral, the activation in our group of adults with autism was confined to the left fusiform region. However, significant activity was also noted on the right in the cuneus, and together these findings again reflect an increase in visual processing demands during emotion processing. It has been suggested that the cuneus may perform some short term storage function, that aids in the short term demands of visual processing (see Chapter Four).

The next area of activation identified for the participants with autism was in the left inferior frontal gyrus (BA 44). The location of this activation was more dorsal and posterior to the activation seen in the controls. In fact, this location in normal adults corresponds to Broca's area. Functional imaging research has demonstrated that this area is engaged when individuals are asked to repeat back words they hear or read out loud (Price et al., 1996). Activation of the left frontal gyrus (BA 44) has also been demonstrated in a regional cerebral blood flow study of short term visual memory using a delayed matching to sample paradigm (Elliott and Dolan, 1998). This activation was noted when the task required participants to remember the colors depicted in each test stimulus, and reflected the use of verbal rehearsal strategies. Similarly, subsequent to a review of activation studies examining working memory, Smith et al. (1998) suggested that one component of verbal working memory is phonological rehearsal which is mediated by the left frontal speech regions BA 44 / 6. We cannot attest to the use of verbal strategies by our participants with autism. During the scan period participants were viewed at a distance, through a window in the control room. It is a possible, therefore, that they engaged in subvocal repetition of the auditory stimulus or verbal problem solving as part of their response strategy.

The second frontal region to demonstrate a significant activation during the emotion matching performance of the participants with autism was a bilateral area of the medial frontal and anterior cingulate gyri. The dual role of the cingulate gyrus in emotion and attention has been discussed above in the review of the female activation results. The performance data for the participants with autism would certainly suggest that the emotion task required increased attentional resources. However, the volume of tissue activated in these findings may correspond more directly to the medial frontal regions than the cingulate gyrus in our

participants with autism. This suggestion is made in light of a recent study that has reported both smaller anterior cingulate volumes on MRI, and lower regional cerebral metabolic rate for glucose in this area in a group of seven adults with autism (Haznedar et al., 1997). Activation of the medial frontal cortex has been reported in a study by Phillips et al. (1997), using facial stimuli conveying disgust. These researchers stated that the association of this area with the orbitofrontal cortex is suggestive of its role in emotional responses to visceral, offensive stimuli. It is notable that in the activation results of our participants with autism we do not see the left inferior frontal activation that was apparent in the results for our normal males. Therefore the medial frontal activation observed here may signify a larger role for this region in emotion processing in autism. The question as to whether the cingulate / medial frontal activation we observed reflects emotion or attention processes, therefore, remains unresolved.

The cross-modal emotion recognition trials also resulted in significant activations of the left and right anterior temporal poles of our participants with autism (right greater than left). It has been noted previously, that this region is engaged when tasks require the use of semantic and/or perceptual knowledge to differentiate between similar objects and categorize them. Functional imaging studies in normal adults have demonstrated anterior temporal activations in response to familiar face recognition (Sergent, Ohta and Macdonald, 1992), visual discrimination of faces and words (Gorno Tempini, 1998) object naming (Price et al., 1996) object categorization (Moore and Price, 1999) and the classification of subordinate relative to basic categories of objects (Gauthier et al., 1997). Activation of this area by adults with autism under the current circumstances, suggests that they accessed categorical perceptual knowledge to guide their decisions about the emotional stimuli. As compared to the controls, activations in the inferior frontal and inferior temporal regions were absent in the data for the participants

with autism. It appears that our participants with autism did not engage the functional network connecting fusiform, temporal, amygdalar and frontal regions in the processing of facial emotion (Streit et al., 1999) in the same way our normal males. This implies that the process of extracting and holding the emotional significance of the stimuli and using this information to guide subsequent actions (the frontal functions) was not carried out by our participants with autism. Instead, they seemed to engage in verbal rehearsal and an assigning of perceptual knowledge to the classification / categorization of the emotional stimuli.

This suggestion is particularly intriguing given of the conclusions of Schultz et al. (2000) who interpreted their observations of no activation of the fusiform area and significant activation of the inferior temporal lobes to signify that their participants with autism had processed face stimuli as if they were objects. There are also parallels to be drawn between the results of our study and the fMRI study of theory-of-mind by Baron-Cohen et al. (1999). In this study, the theory-of-mind task required that participants examine the area of the face containing the eyes, and select the best descriptor of mental state, for example; concerned or sympathetic. Though frontal activation was recorded for the adults with autism, it was reduced in comparison to the controls. Furthermore, controls were distinguished from the adults with autism by significant power of activation in the left inferior frontal, amygdala and insula. The autism group did not appear to perform the theory-of-mind task with the amygdala, and instead placed greater processing load on the superior temporal gyrus. In another theory-of-mind study, Happe et al. (1996) noted that their participants with autism had engaged areas of the frontal cortex that were different from controls, and concluded that frontal processing in autism was less extensive. These studies and the current study suggest that the functional organization of the limbic-frontal network in autism is disrupted.

The idea that our participants with autism used perceptual knowledge to categorize emotional stimuli is consistent with the observations by Capps, Yirmiya and Sigman, (1992) who suggested that individuals with autism employ cognitive strategies and prototypical examples of emotions to compensate for limited abilities in understanding emotion. Capps, Yirmiya and Sigman, (1992) found that when children with autism were asked to provide personal experiences that exemplified a number of emotions, their tendency to call on references to protypical events proved to be an adequate strategy for simple emotions (happy and sad) but inadequate for complex emotions like pride or embarrassment which required a reference to an audience and social evaluation. It was proposed that poor joint attention and theory-of-mind capabilities in autism contribute to limited experience with complex emotions and result in fewer experiences to recount (Capps, Yirmiya and Sigman, 1992).

The use of prototypes and perceptual knowledge to guide decisions about emotion may also underlie observations that children with autism are more likely to sort pictures containing facial affect according to some non-emotion dimension like type of hat rather than according to emotion (Weeks and Hobson, 1987). Sorting according to object class may be more immediate for children with autism, whereas normal developing children past the age of five seem to naturally engage in referencing the emotions of others and tend to sort according to the emotional dimensions of stimuli (Weeks and Hobson, 1987; Gillbert, 1969). Karmiloff-Smith et al. (1995) have suggested that in normal development the cognitive processes involved in emotion recognition and mentalizing (making theory-of-mind judgements) become largely automatic. Furthermore, Buitelaar and van der Wees (1997) have recently suggested that these processes are subserved by common circuits in the frontal lobes. As our findings suggest, individuals with autism may not engage the inferior frontal regions and as a result, engage in cognitive strategies that emphasize categorization and past perceptual knowledge.

6.1.3.2. CROSS-MODAL PROCESSING OF EMOTION

Bryson (1972) identifed that children with autism have significant impairments in the ability to form sensory cross-modal associations. It has been suggested that disturbances in attention lead to abnormalities in cross-modal integration, and imitation in autism (Smith and Bryson, 1994). It has been further proposed that in autism there is a failure by the amygdala to assign emotional and motivational salience to sensory events which makes the process of shifting from one sensory modality to the next extremely discordant. Calvert et al. (2000) have reported increased anterior cingulate activation in normal adults during cross-modal processing where the visual stimulus (a person's lips moving while reading) and auditory stimulus presented (someone reading aloud) are discrepant. They suggested that the activation of the cingulate gyrus reflected the need to deflect attention to one or another modality in order to process the interfering stimuli (Calvert et al., 2000). Our observation of anterior cingulate activation during cross-modal emotion trials in our participants with autism, then, may indicate that they processed our auditory and visual stimuli as though they were competing rather than complementary sensory experiences. This suggestion seems consistent with observations that children with autism tend to process multimodal sensory stimuli one modality at a time (Bryson, 1972).

Distortions in cross-modal integration may lead to the formation of highly idiosyncratic and situation specific representations of experiences in autism (Waterhouse, Fein and Modahl, 1996). Children with autism are often attributed with particularly good rote memory skills. However, Bennetto, Pennington and Rogers (1996) have shown that the recall of word lists by children with autism will often include semantically similar words and additional words within the same semantic category, indicating deficits in the way source memories are laid down.

It has been proposed that the formation of fragmented cross-modal associations underlie the difficulties that individuals with autism have in understanding and learning from social interactions (Waterhouse, Fein and Modahl, 1996). In a recent study, Beversdorf et al. (1998) have identified that the recall of normal adults improved when the semantic content of to-be-remembered sentences was high in emotion as opposed to neutral. High functioning adults with autism, in contrast, failed to show the same improvement and, in fact, showed decreased recall for emotionally laden material. These observations are consistent with the view that in autism there is a failure by the amygdala to assign affective salience to new sensory records (Waterhouse, Fein and Modahl, 1996). The availability of poorly integrated, narrowly defined memory traces may help to explain why people with autism display an insistence on sameness, a dependance on external cues, and difficulties with generalization. Taken to the other extreme, the savant skills reported in some individuals with autism seem to rely on highly developed abilities in classifying and identifying the components of patterns and in remembering predictable pattern structures (Pring, Hermelin and Heavey, 1995; Young and Nettelbeck, 1995). These heightened abilities appear to draw on perceptual knowledge and categorization in much the same way as our participants with autism approached the emotion recognition task.

6.1.4. CONCLUSION

We studied a group of high functioning young adult males with autism using $H_2^{15}O$ PET

to identify the neuronal areas activated during the performance of a cross-modal emotion

recognition task. The cross-modal matching of emotion, as compared to gender matching,

resulted in left fusiform activation in the participants with autism. We suggested that these

findings were consistent with previous research linking this region to face processing and

reflective of greater demands for the extraction of facial information during emotion matching

as compared to gender matching trials. In addition, cross-modal matching of emotion by the

participants with autism resulted in significant activation on the left in Broca's region of the

inferior frontal gyrus, bilaterally in the anterior cingulate region and bilaterally in the anterior

temporal poles. The observation of activation in Broca's area in the participants with autism

was thought to result from subvocal verbal problem solving. The observation of anterior

cingulate activation in these participants was suggested to reflect either emotion processes or

attention processes engaged during the cross-modal processing of emotion. Finally, the

bilateral activation of the anterior temporal poles was thought to indicate that the participants

with autism had accessed an area of the brain that is associated with object categorization and

perceptual knowledge in order to perform the emotion matching task. It was concluded that

the results for the controls were consistent with research demonstrating a functional network

that calls upon inferior frontal, temporal and amygdalar regions in the processing of emotion.

In contrast, the participants with autism appeared to engage a network that emphasized verbal

problem solving and the assignment of perceptual knowledge to the classification and

categorization of the emotional stimuli.

CHAPTER SEVEN

7.1 BETWEEN-GROUP ANALYSES

The results reported in Chapters Four, Five and Six concern within-group analyses. Friston (1997) has noted that to date, most functional PET studies have used this type of analysis. Indeed, previous reports on emotion recognition (eg. George et al., 1993; Blair et al., 1999; Nakamura et al., 1999; Morris et al., 1996; Narumoto et al., 2000) and emotional prosody (George et al., 1996a; Buchanan et al., 2000) have outlined the findings from within-group analyses, and therefore serve as appropriate comparison points to our results in these chapters. Within-group analyses identify the areas of activation associated with the cognitive dimension under study, and relate specifically to the group that is examined. The inferences drawn in such studies are generally extended to a larger population group through independent replication.

It is possible to do intergroup comparisons by first running separate analyses of each group and then examining the list of activation areas identified for each one. However, the results from this type of comparison are open to alternate interpretations. For example, the observation of activation in one area for one group and no activation of the same locale for another group may reflect greater variability in the measurements collected for the second group (and as a result lower statistical scores), or systematic differences in brain anatomy that lead to a shift in the stereotaxic location of activations, or real group differences that are not reflective of the populations from which they were drawn (i.e., groups drawn from different

ends of a continuum) (Woods et al., 1996). Finally, comparing the separate analysis results for

two groups does not permit a formal comparison of one group with another. To do this, it is

necessary to conduct a between-group analysis. Where more than one group is examined under

the same experimental protocol, it is possible to conduct between-group comparisons (Woods,

1996). In studies such as these, both within-group and between-group analyses are typically

used to explore the data. For example, George et al. (1996a) reported within-group and

between-group results in their PET study of sex differences in self-induced mood changes.

Between-group analyses permit the extension of findings to population groups and may

be conducted using the Statistical Parametric Mapping (SPM) package (Friston, 1997).

Inferences about a group under study are drawn from analyses that treat participant identity as

a random effect. The random-effects analysis explicitly accounts for the possibility that the

differences between two groups could have resulted from the random selection of participants

from opposite ends of a single distribution. The error term in random-effects analysis is

identified by the variability in activation effects from participant to participant. Significant

activations identified using this analysis relate to areas that have been activated in much the

same way in all of the participants. Consequently, the random-effects model permits the

extension of inferences to the population from which participants have been drawn.

However, in random-effects analyses it is the number of participants that determines the

number of degrees of freedom, and study groups of ten to twenty participants may be

necessary to identify significant group differences (Woods, 1996). Within the context of the

analysis of our studies, this fact makes it all the more important to examine within-group

results first before moving to between-group analyses.

Random-effects analyses in SPM are carried out by taking the contrasts of parameters

estimated in a first-level (within-group) analysis and entering them into a second group

comparison where the error term is calculated from participant-by-participant variability.

This entails the entry of image sets (realigned, transformed and smoothed) for each participant

into a single subject with conditions analysis of covariance in SPM. Contrasts for the condition

effects (eg., Emotion - Identity) are identified, and individual Statistical Parametric Maps are

created for each participant. A product of this analysis is a contrast image and header.

The contrast images from two groups are then entered into the second analysis, typically, a

two-sample t-test from which contrasts identify the significant group effects.

The results from a within-group analysis pertain to a contrast of the changes in rCBF

observed between an activation task and a baseline task for one group of participants.

A random-effects analysis begins with the results from this type of contrast (though on a

individual participant basis) and compares one group with another to identify significant group

differences. Areas identified as significant in within-group analyses will not necessarily

distinguish between two groups in a random-effects analysis. Figure 30 illustrates this point.

A selection of the within-group results for two groups A and B are depicted graphically, and the

locations exceeding the significance threshold would be identified as significant areas of

activation on the conventional three dimensional SPM t-map. When both conditions are

mapped, it is possible to identify a number of between-group results that might be identified in

random-effects analysis.

Figure 30.
Symbolic Representation of Within-Group and Random-Effects Results

Group A Section of SPM. map contrasting two conditions

SPM Intensity

significance Threshold

SPM Position

Group B Section of SPM. map contrasting two conditions

SPM Intensity

significance Threshold

SPM Position

Groups A and B - Identification of Significant Between Group Differences

SPM Intensity

SPM Position

A   B   C   D   E
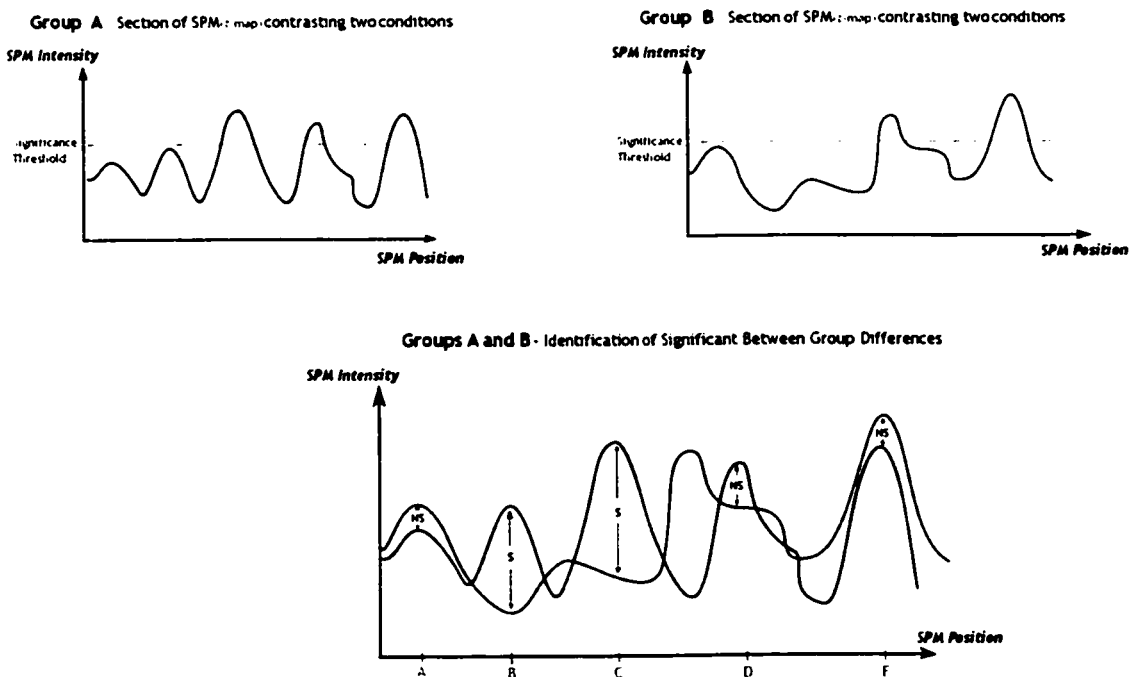
In the lower graph, SPM position A, identifies no significant within-group or random-effects results. SPM position B illustrates the case where no results would be identified in within-group analyses, but there is a significant between-group difference. At SPM position C there is a significant within-group result for Group A and a significant difference between the groups in the between group results. At SPM position D, a significant within-group result is observed for Group A, but in the random-effects analysis no group difference is identified. Finally, at SPM position E, both groups show a significant within-group and no significant between-group result. These examples demonstrate that it is possible to identify instances where within-group results cancel each other out, and instances where group differences are

identified in regions that are non-significant in within-group analyses. This is because it is the

relative difference in SPM intensities that identifies significant group differences in the random-

effects analysis. This example also serves to illustrate the importance of exploring within-

group results first, as they relate more closely to the processing demands of the cognitive

dimension under study. The results from the within-group analysis then, provide a framework

for exploring the between-group results.

7.1.1. STUDY I VISUAL EMOTION RECOGNITION BETWEEN THE SEXES

Directly comparing the changes in rCBF associated with visual emotion recognition

(emotion - identity) in males and females revealed significant activation of the right medial

frontal gyrus and right superior occipital gyrus in males, and the left inferior frontal gyrus, right

amygdala, and left fusiform gyrus in females (Figures 30 and 31 and Table 12).

Table 12.
Between-Group Results for Activations Associated with Visual Emotion Recognition

Group Subtraction	Brain Location according to Talairach	Talairach Coordinates x,y,z (mm)			Brod mann Area	t value	p value uncorrected
Male > Females	R Medial Frontal Gyrus	4	70	10	10	4.43	p < 0.001
	R Superior Occipital Gyrus	34	-84	42	19	4.20	p < 0.001
Females > Males	L Fusiform Gyrus	-28	-60	-22	37	6.42	P < 0.001
	R Amygdala	24	-8	-16	Am	5.06	p < 0.001
	L Inferior Frontal Gyrus	-24	42	-14	47	4.24	p < 0.001

Figure 31. Study I: Between-Group Results

Areas activated greater by women than men during visual emotion matching

left sagittal   right sagittal   medial sagittal

ventral transverse   dorsal transverse   posterior coronal   anterior coronal

① R Amygdala
② L Inferior Frontal Gyrus
③ L Fusiform gyrus
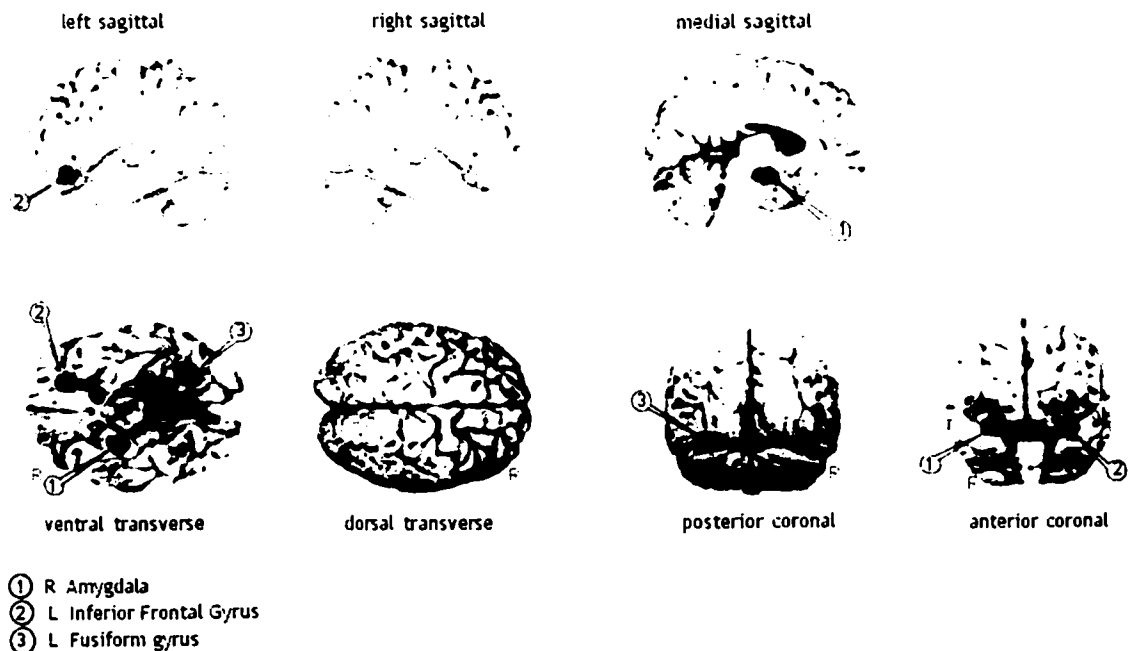
Figure 32. Study I: Between-Group Results

Areas activated greater by men than women during visual emotion matching

left sagittal   right sagittal   medial sagittal

ventral transverse   dorsal transverse   posterior coronal   anterior coronal

① R Medial Frontal Gyrus
② R Superior Occipital Gyrus
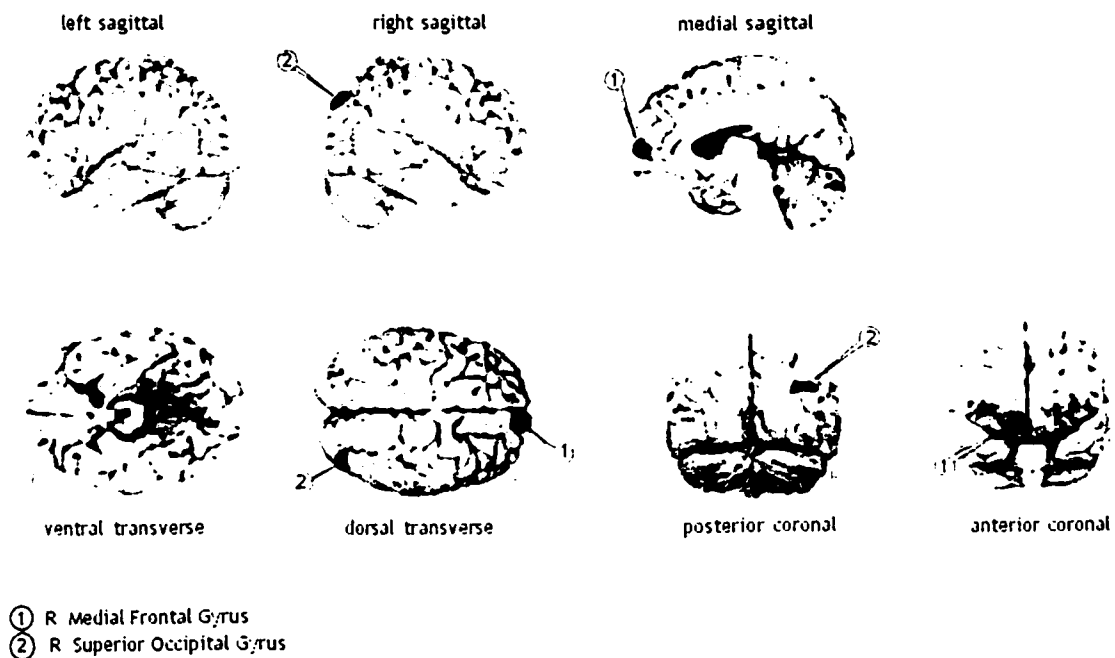
Activation of the right inferior frontal cortex was noted in the within-group results for visual emotion recognition (Chapter Four) in both males and females. As this area was commonly activated by both groups, it is reasonable to expect that in a comparison of the two groups it would not distinguish between them. In contrast, left inferior frontal activation was reported in the within-group analysis of the female data only. In the random-effects analysis, the left inferior frontal region showed significantly greater activation in females than in males. These results identify that for visual emotion processing the localization of function within the frontal lobes is more bilaterally distributed in females than in males.

These results also lend support to the conclusion that during visual emotion processing females activated a broader network of areas than did our males. This assertion is also supported by the observation that the areas showing greater activation in males than females were confined to the right hemisphere. The observation of greater left fusiform activation in females than males is also consistent with the idea of activation of a broader network of regions in females. In addition, a greater right over left distribution of fusiform activation has been noted in some face processing studies (Haxby et al., 1994: Puce et al., 1995). The identification of greater left fusiform activation , therefore, may also suggest more bilateral distribution of the early stages of face processing in females. It also suggests that females may have placed greater processing emphasis on the extraction of facial information than males.

Finally, the rCBF associated with facial emotion processing by females was also distinguished from that identified for males by significantly greater activation of the right amygdala. Activation of the amygdala has been reported with the processing of expressions of sadness (Blair et al., 1999) and fear (Phillips et al., 1997). The PET study by George et al. (1996a) used self-induced mood changes and pictures of facial affect to identify sex differences

in emotion processing. They found that women demonstrated greater activation than men in

the left inferior frontal, left midfrontal and areas of the basal ganglia with transient self-

induced sadness. George et al. (1996a) concluded that females had activated a wider portion

of their limbic system than did men during transient sadness. Our findings appear to concur

with those of George et al. (1996a) and identify greater activation of limbic structures by

females despite similar performances on the emotion matching task.

7.1.2. STUDY II: PART A.

CROSS-MODAL EMOTION RECOGNITION BETWEEN THE SEXES

Directly comparing the activations associated with cross-modal emotion matching in

males and females revealed that males had activated the left inferior frontal gyrus and left

inferior parietal gyrus more than females. In contrast, females more than males, showed

greater activation of the left thalamus, right fusiform and left anterior cingulate gyrus.

Table 13.
Between-Group Results for Activations Associated with Cross-Modal Emotion Recognition
in Men and Women.

Group	Brain Location according to Talairach	Talairach Coordinates x,y,z (mm)			Brod mann Area	t value	p value uncorrected
Males > Females	L Inferior Frontal gyrus	-34	38	-14	47	4.88	p < 0.001
	L Inferior Parietal	-40	-39	35	40	3.68	p = 0.001
Females > Males	L Thalamus	-16	-26	12	P	4.24	p < 0.001
	R Fusiform gyrus	36	-72	-4	19	4.12	p = 0.001
	L Anterior Cingulate	-14	28	36	32	3.59	p = 0.001

Figure 33. Study II: Between-Group Results

Areas activated greater by women than men during cross-modal emotion matching

left sagittal   right sagittal   medial sagittal

ventral transverse   dorsal transverse   posterior coronal   anterior coronal

① L Thalamus   ② R Fusiform gyrus
③ L Anterior Cingulates
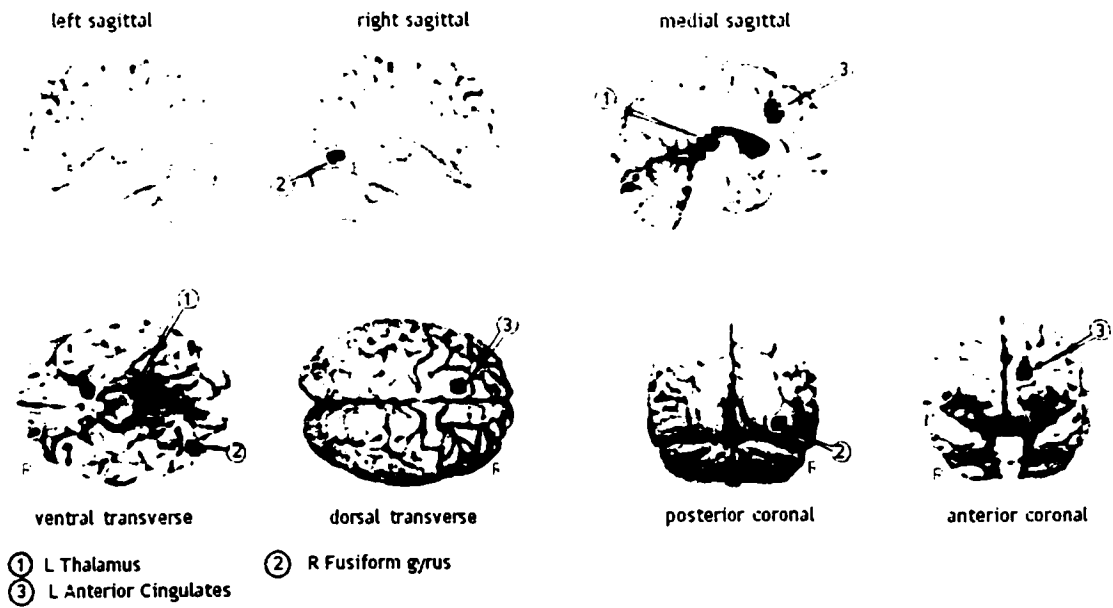
Figure 34. Study II: Between-Group Results

Areas activated greater by men than women during cross-modal emotion matching

left sagittal   right sagittal   medial sagittal

ventral transverse   dorsal transverse   posterior coronal   anterior coronal

① L Inferior Frontal gyrus
② L Inferior Parietal gyrus
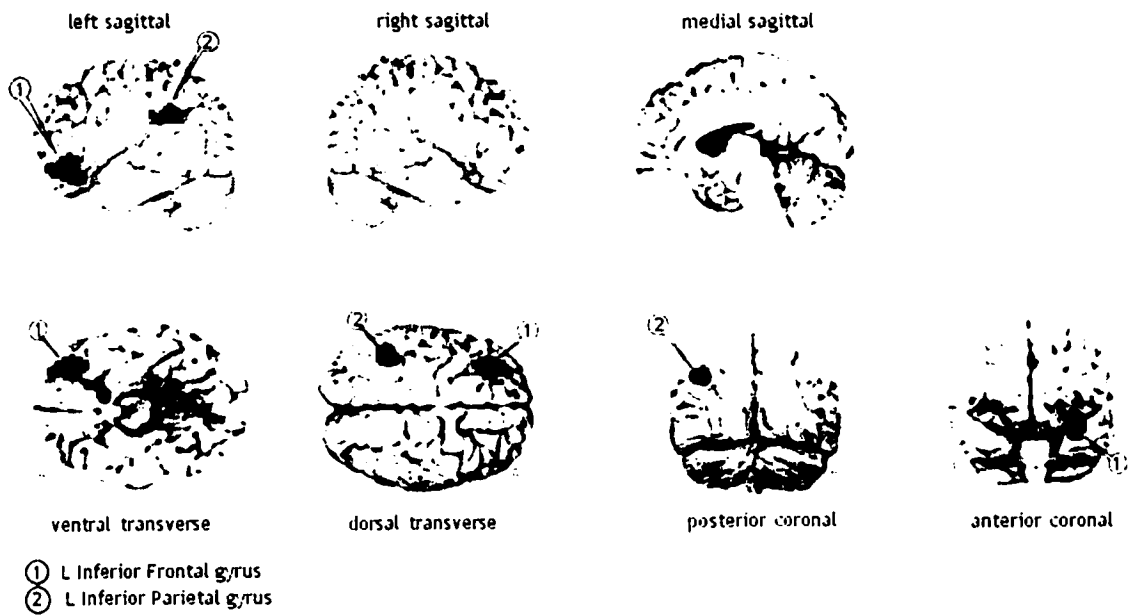
The changes in rCBF associated with cross-modal processing of emotion in males were distinguished from that identified for females by greater inferior parietal activation. Previously, activation of the inferior parietal cortex was noted in the within-group analysis for males, however, this activation was located in the right hemisphere, not the left. The inferior parietal region is one of a number of polymodal convergence zones of the cortex (eg. superior temporal, intraparietal sulci, lateral prefrontal cortices and the amygdala). The cerebral functions associated with this region include the integration of spatially and temporally distributed polymodal sensory inputs (Kolb and Whishaw, 1990; Mesulam, 1998). Therefore, greater parietal activation in males, as compared to females, may signify the recruitment of different multimodal convergence areas during cross-modal emotion matching.

The observation of left inferior frontal activation in males is consistent with the results from the within-group analysis of the male cross-modal data. It has been recently suggested that this area is engaged when individuals must make decisions in uncertain situations, or based on partial information (Elliot, Dolan and Frith, 2000). Research that has examined visual emotion recognition has stressed the participation of inferior frontal regions in the evaluation and experience of emotion (eg George et al., 1993; Naramoto et al., 2000). Thus it appears that one of the regions where males demonstrate greater activation than females is localized to an area that is important in the assembly and evaluation of an integrated emotional experience.

For our female participants, the right fusiform gyrus was among the regions that showed greater activation as compared to males. These results suggest that our females may have placed greater processing emphasis on the extraction of facial information during the performance of cross-modal emotion matching. In the within-group analysis of cross-modal

emotion processing for females, we noted activation in the right superior temporal cortex.

Similar activation was noted in the random-effects analysis, however these results failed to

reach our cut-off for establishing significance ($t = 3.24$ p $= 0.003$).

Activations in the left thalamus and left anterior cingulate gyrus also differentiated

cross-modal emotion processing in females from males. Other functional imaging studies of

emotion processing have reported significant activation of these regions. For example,

Naramoto et al. (2000) identified thalamic activation among a number of regions activated by

facial emotion recognition (in contrast to a baseline rest condition). Phillips et al. (1997) also

reported thalamic activation when individuals viewed faces depicting the emotion disgust.

In addition, anterior cingulate activations have been reported in imaging studies using facial

emotion and emotionally charged stimuli (George et al., 1993; Lane et al., 1997; Morris et al.,

1998). Finally, Buchanan et al. (2000) reported left cingulate activation with the processing of

emotional prosody. Interconnections between these structures form part of a feedback loop

that links the amygdala to the cortex, where the amygdala projects efferent to the thalamus,

which projects to the anterior cingulate cortex, which in turn sends efferent back to the

amygdala. This feedback loop is thought to participate in emotion processing by guiding

adaptive behavioral responses to events (Chua and Dolan, 2000). With reference to the

anterior cingulate cortex in particular, it has been suggested that this region plays an

important role in assessing the motivational content of internal and external experiences, and

in the regulation of context dependent behaviors (Devinsky et al., 1995). Lesions to this area

can produce changes in mood states, anxiety, apathy, indifference or akinetic mutism (Fuster,

1999). Through its rich interconnections with the amygdala, the anterior cingulate appears to

be active in assigning motivational and behavioral significance to incoming stimuli (Heilman et

al., 1994). To do this it may be necessary to reference previous experiences

(reward/motivation) and pool the current internally and externally driven emotional states.

However, the cingulate gyrus is also important in attentional processes. There are extensive projections linking the anterior cingulate with the dorsolateral frontal lobe and the inferior parietal lobe (Heilman et al., 1994) and it is suggested that the anterior cingulate participates in attention processing when the selection of a response is required (Posner, 1994). The anterior cingulate region may also assist in deflecting attention toward one or another sensory modality in aid of response selection under conditions of discrepant cross-modal input (Calvert et al., 2000). It appears therefore, that the anterior cingulate activation for our females can be explained by the association of this area with emotion processes, attention processes or both.

It was observed that during cross-modal emotion matching, there was greater activation of the fusiform area for our female participants than our male participants. These results parallel those reported in the between-group comparison of males and females in our first study of visual emotion recognition. These findings would suggest that females, in contrast to males, place greater processing emphasis on the extraction of facial information in tasks that use facial emotion stimuli. A second observation that is shared with the between-group results for the first study, concerns the distribution of processing across the hemispheres. While our females showed greater activation than our males in structures in both hemispheres, the activations that were greatest for males were localized to either the right or left hemispheres (Study I and Study II respectively). These results are also consistent with the conclusions drawn from the within-group analyses for males and females, suggesting that the functional network of regions engaged in the processing of emotion is more broadly distributed, and less lateralized in females than males, and point to sex differences in the cross-modal

processing emotion.

Turning to the frontal cortices, we found that males demonstrated greater activation of the left inferior frontal cortex, while females had greater activation of the anterior cingulate gyrus. Both of these regions have been ascribed with a functional role in emotion processing. Females appear to have placed greater processing emphasis on referencing previous experiences, assessing the motivational content of the current experience, and / or directing attention to the appropriate cross-modal input to facilitate response decisions. Males, in contrast, appear to have placed greater emphasis on the construction of an internal representation from which the emotional state of the individual is regulated and decisions or actions are guided. (Frith and Dolan, 1997). Stated another way, our males appear to have relied less on experiential and motivational characteristics of the stimuli and more on processes necessary to generate a response. While our study failed to demonstrate a superiority for emotion processing in women, studies with larger study groups have identified sex differences in emotion recognition (Erwin et al., 1992). Perhaps for the male, relating less to the motivational and experiential qualities of stimuli results in a less effective method of disambiguating the subtleties of facial emotion.

7.1.3. STUDY II: PART B. CROSS-MODAL EMOTION RECOGNITION BETWEEN CONTROLS AND ADULTS WITH AUTISM

Figure 35. Study II: Between-Group Results

Areas activated greater by Controls than Participants with Autism during cross-modal emotion matching

left sagittal   right sagittal

ventral transverse   dorsal transverse   posterior coronal   anterior coronal

① L Inferior Frontal gyrus   ② R Fusiform gyrus
③ L Lingual gyrus
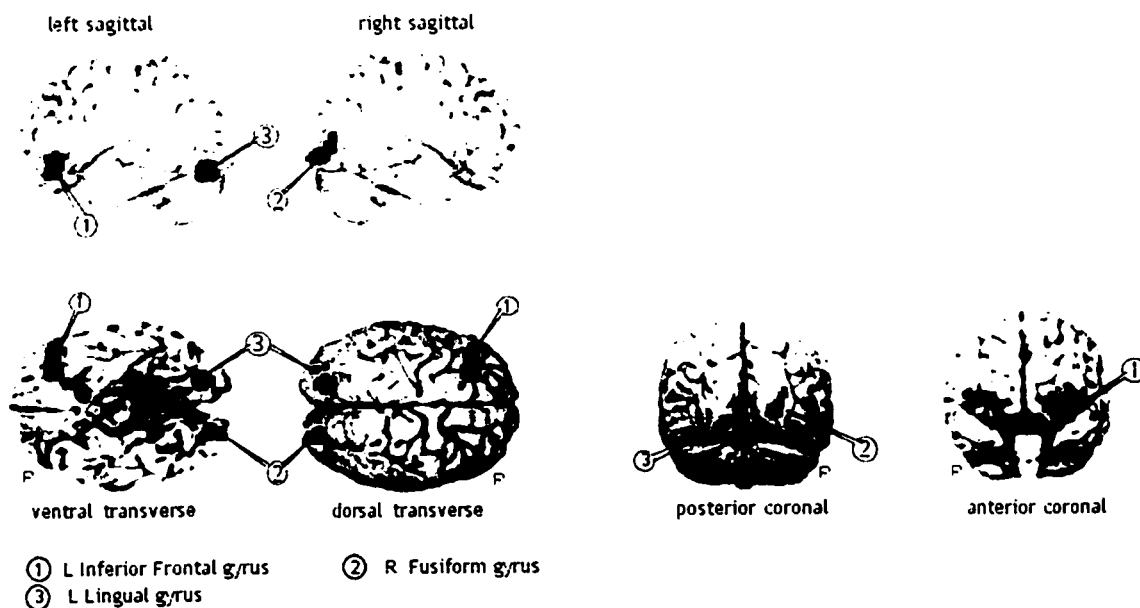
Figure 36. Study II: Between-Group Results

Areas activated greater by Participants with Autism than Controls during cross-modal emotion matching

left sagittal   right sagittal   medial sagittal

ventral transverse   dorsal transverse   posterior coronal   anterior coronal

① R thalamus   ② R Anterior Temporal Pole
③ L Anterior Cingulate gyrus
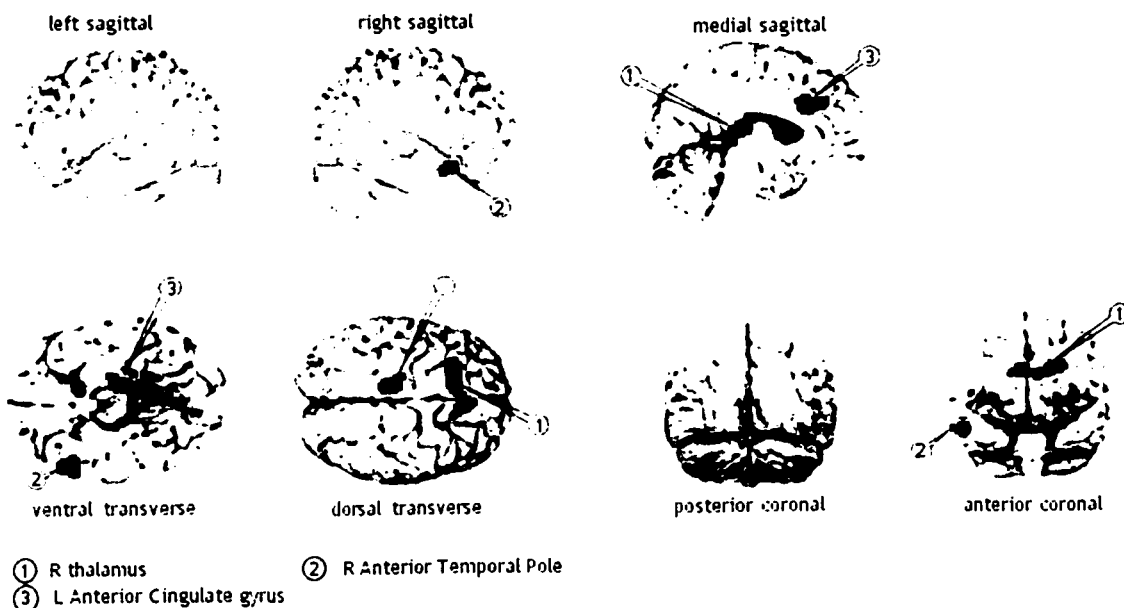
Table 14.
Between-group Results for Activations Associated with Cross Modal Emotion Recognition
in Controls and Adults with Autism.

Group Comparison	Brain Location according to Talairach	Talairach Coordinates x,y,z (mm)			Brod mann Area	t value	p value uncorrect ed
Control > Autism	L Lingual gyrus	-18	-78	-10	19	4.30	p < 0.001
	L Inferior Frontal gyrus	-34	40	-10	47	4.25	p < 0.001
	R fusiform / cuneus	24	-81	2	19	4.11	p = 0.001
Autism > Control	R thalamus	-12	-21	12		4.55	p < 0.001
	R Anterior Temporal Pole	56	22	-16	38	3.77	p = 0.001
	L Anterior Cingulate	-12	29	26	32	3.73	p = 0.001

Differences existed in the activation patterns associated with cross-modal emotion recognition between controls and men with autism. Controls had greater rCBF in the left lingual gyrus, the right fusiform gyrus and the left inferior frontal cortex compared to males with autism. In contrast, the participants with autism, more than control males, demonstrated increased rCBF in the right thalamus, right anterior temporal pole and left anterior cingulate gyrus during cross-modal emotion processing.

The greater activation of the inferior temporal regions by our controls suggests that they may have conducted a more thorough analysis of the facial stimuli than our participants with autism. This suggestion is consistent with previous imaging research on autism, where it has been observed that adults with autism failed to activate the fusiform area during the processing of facial features, and instead activated inferior temporal regions more commonly associated with object recognition (Shultz et al., 2000). Furthermore, a recent imaging study of facial emotion processing by Critchley et al. (2000) identified greater left lingual activation

for adults with autism which contrasted with greater right fusiform activation in controls.

Critchley et al. (2000) suggested that relative to the controls, adults with autism had failed to

activate the cortical regions associated with the processing of faces during the processing of

facial emotion. Together with these findings, our results suggest that emotion processing

deficits in autism are at least in part due to deficiencies in the initial processing of facial

stimuli.

The second area in which cross modal emotion matching was associated with greater

rCBF in controls than adults with autism was the inferior frontal cortex. These results were

similarly reflected in the within-group analysis for the control group. These findings suggest

that our participants with autism placed relatively less processing emphasis on the assembly of

an internal emotional representation and less regulation and preparation of a response than our

male controls. On first glance these results would appear to concur with those of Critchley et

al. (2000), indicating limbic activation (amygdala) with implicit processing of facial emotion in

controls, and not in adults with autism. Critchley et al. (2000) suggested that their findings

signified a dysfunction, in autism, of the pathways linking the limbic and paralimbic,

cerebellar, and extrastriate visual regions. However, our adults with autism demonstrated

significantly greater activation than our controls in the anterior cingulate cortex and the

thalamus. These areas were discussed earlier, with reference to emotion processing facilitated

through a feedback loop linking the amygdala to the frontal cortices. Thus it appears that

while the activation pattern for our participants with autism distinguished them from the

controls, the location of two of these activations were found in areas that can be associated

with emotion processing. However, the anterior cingulate also participates in attention

processing when the selection of a response is required and may assist in directing attention

during cross-modal processing (Posner, 1994; Calvert et al., 2000). It appears, therefore, that

the anterior cingulate activation for our participants with autism may be explained by the association of this area with emotion processes, attentional processes or both.

It is worth noting that our participants with autism were able to successfully perform many of the emotion matching trials. However, they did make significantly more errors than the controls. These findings contrasted with similar performances for the two groups on cross-modal gender recognition trials. Arguably, both tasks demanded an analysis of facial features. Therefore, the poorer performances on the emotion trials by the adults with autism is suggestive of further disruption of the functional network that subserves cross-modal emotion processing. This suggestion is supported in particular by the observation that the right anterior temporal pole showed greater activation in the adults with autism relative to controls. Bilateral activation of the anterior temporal poles, right greater than left, was observed in the within-group analysis for the participants with autism. This region appears to be important in perceptual knowledge, object naming and categorization (Price et al., 1996; Gauthier et al., 1997; Moore and Price, 1999). Activation of this area during cross-modal emotion matching by adults with autism suggests that they accessed categorical perceptual knowledge to guide their decisions about the emotional stimuli. The need to draw on this knowledge may point to an insufficiency in the frontal processes responsible for creating an integrated emotional experience and guiding subsequent decisions based on this experience. This suggestion is consistent with the observation of greater activation of the inferior frontal cortex in controls.

7.1.4. CONCLUSION

The random-effects analyses conducted on the data from Studies I and II permit the direct comparison two study groups (eg. male and female) and identifies areas of activation that significantly distinguishes between the groups. The random-effects analysis allows the inferences about a group under study to be extended to the population from which they were selected.

Direct comparison of the increases in rCBF associated with visual emotion recognition in Study I, identified differences in the activation patterns of males and females. Females were found to have greater activation of the left fusiform right amygdala and left inferior frontal region than males. Males, in contrast had significantly increased rCBF in the right medial frontal gyrus and right superior occipital gyrus, as compared to females. It was noted that right inferior frontal activations were identified in the within-group analysis of both male and female participants. As such, the identification of greater left inferior frontal activation in females suggests that the localization of function for visual emotion processing is more bilaterally distributed within the frontal lobes of females than males. The observation of greater left fusiform activation in females than males identifies that females may have placed greater processing emphasis on the extraction of facial information than males. Furthermore, observations of greater activation of the amygdala by females, points to a greater engagement of limbic structures by females during facial emotion processing. These results suggest that females activate a broader network of areas than males during the processing of emotion. Further support for this suggestion was found in the observation that greatest activations in males, as compared to females, were confined to the right hemisphere.

In Study II, direct comparisons of the male and female data for cross-modal emotion recognition identified differences in the activation patterns between the sexes. Males, more than females, had greater activation of the left inferior frontal gyrus and left inferior parietal gyrus, whereas females more than males, activated the the left thalamus, right fusiform and left anterior cingulate gyrus. It was suggested that the observation of greater left inferior frontal activation in males was consistent with the results from the within-group analysis for males, and suggestive of greater processing emphasis being devoted to the assembly and evaluation of an integrated emotional experience by males. For females, greater activation of the anterior cingulate gyrus was discussed in terms of greater processing emphasis being devoted to referencing previous experiences, assessing the motivational content of stimuli, and / or directing attention to the appropriate cross-modal input to facilitate response decisions.

Between group results for the autism and control groups in Study II revealed significant differences in the activations associated with cross-modal emotion processing. The control males were distinguished from the autism group by greater activation of the left lingual gyrus, the right fusiform gyrus and the left inferior frontal cortex. In contrast, adult males with autism, more than control males, demonstrated greater activation of the right thalamus, right anterior temporal pole and left anterior cingulate gyrus during cross-modal emotion processing. These findings suggest that relative to the controls, our adults with autism placed relatively less processing emphasis on the extraction of facial information and on the assembly and evaluation of an integrated emotional experience. The results also indicated that our participants with autism had engaged functional areas concerned with assigning motivational content to experiences and/or directing attention to cross-modal sensory input. Finally, it was suggested that greater activation of the right anterior temporal pole by the participants with autism signified the use of categorical perceptual knowledge to guide decisions about the emotional stimuli.

CHAPTER EIGHT

8.1 FUTURE DIRECTIONS

We have identified the location of activation foci associated with the processing of

emotion in faces and with cross-modal matching of vocal prosody to visual facial emotion in

men and women. The regions in which activations were demonstrated were consistent with

findings in other functional imaging studies on emotion. Our results suggest, however, that

more attention should be paid to the composition of study groups in imaging studies,

particularly those examining emotion and/or other cognitive processes that may distinguish

between the sexes. The use of a relatively small number of young adults limits the extent to

which these results can be generalized on the whole to men and women and a result,

replication of these findings is needed.

New to functional studies on emotion, is the cross-modal task employed here, and

further research is needed to explore the relative contribution of each sensory modality in the

cross-modal processing of emotion. This could be achieved using a protocol similar to the

current one, with separate task conditions requiring auditory, visual and cross-modal emotion

matching. Alternately, cross-modal tasks could be designed to change in the processing

demands along one dimension (e.g. visual) across the eight or nine blocks of trials so that

performance measures could be used as covariates of the observed changes in regional cerebral

blood flow. Another extension of the current research would make use of MEG and PET or fMRI

to examine the temporal nature of activations. Finally, the association drawn between our findings for women in the cross-modal study and the morphology of the sylvian fissure and posterior callosal areas suggests that this task may be applicable to functional imaging studies of handedness and sexual orientation (Witelson, 1989; Witelson and Kigar, 1992; McCormic and Witelson, 1994; Davatzikos and Resnick, 1998).

Turning to autism, our findings suggest that the difficulties that individuals with autism have in recognizing and understanding emotions may be due, in part to a reliance upon specific examples or prototypical representations of emotions and the use of perceptual / categorical knowledge to understand or problem-solve new experiences. At the root of this approach may be a failure to draw together and evaluate an integrated emotional experience.

This framework may help to account for some of the other characteristic behaviors of autism, such as the insistence on sameness, difficulties with generalization, poor empathy skills and difficulties taking the perspective of others, and, assist in the design of treatment strategies. Social experiences may not hold the same intrinsic value for the child with autism as they do for the rest of us, and therefore our efforts in treatment should focus on providing a rich and varied social environment in which the value of social experiences is demonstrated over and over in ways that are reinforcing for the individual child.

To extend the present findings in autism, future research may be directed along a number of lines of inquiry. It may be of interest to examine the anterior temporal lobe functions of individuals with autism, particularly with reference to the categorization of multi-modal experiences. Further inquiry targeting this region could explore the savant skills exhibited by some individuals with autism.

The need for further studies of the limbic system in autism are also suggested by the current research findings. The neurotransmitter serotonin plays an important role in the limbic system. One possible direction for research, therefore, would use PET with radioligands such as setoperone to visualize the distribution of serotonergic neurons in the brain of a group of adults with autism and normal controls (Kapur et al., 1997). Other studies could examine changes in regional cerebral blood flow in autism and controls with the administration of subanaesthetic levels of Nitrous Oxide (Gyulai et al., 1996) or drugs that act as serotonin agonists such as d-fenfluramine (Meyer et al., 1996).

Our findings also suggest a need to broaden the examination of frontal functions in autism. Functional imaging research has begun to explore capacities like theory-of-mind (Happe et al., 1996) and future work could focus on flexibility of thought, imagination or responses to nonverbal or interpersonal cues. The activation of the anterior cingulate region by our participants with autism during the cross-modal emotion task raises questions regarding the effective allocation of attention in autism, particularly under circumstances involving cross-modal integration. It would be of interest to examine the attentional processes of individuals with autism using functional imaging methods.

Finally, the present research indicates that attempts to train or remediate the deficits in understanding emotion found in autism would have limited success when directed toward empathy skills, introspection or the appreciation of the emotions of others. Instead, our findings suggest that training should provide many examples of emotions, and focus on the identification of cues that help distinguish between and categorize the emotional displays of others.

The above discussion serves to illustrate but a few of the possible future directions and exciting possibilities raised by this research. Ultimately, the pursuit of these and other converging lines of inquiry will lead to a better understanding of the neurological foundation of autism.

Appendices

Appendix A. Study Consent Form

CONSENT FORM FOR PDD/AUTISM AND PET SCAN STUDY
(Drs G. Bartolucci, C. Nahmias, and L. Wahl, McMaster University)

I _____ consent to have a PET study done on myself. It has been explained to me that I will have 9 injections of a very small amount of radioactive oxygen in water. The radioactivity disappears in less than 20 minutes.

An intravenous (i.v.) will be placed in a vein in my arm by a trained nurse or technologist and attached to a tube carrying a small amount of saline (a normal body fluid) to keep the vein open. A small dose of radioactive water (10mCi) will be inserted into the tube every 15 minutes, for a total of 9 times. I will be asked to press a button with either my left or my right hand in response to images that will appear on a computer monitor positioned in front of me while I am in the tomograph. I will be asked to identify whether the picture on the right or left of the screen matches the picture in the centre of the screen.

I understand that in any study such as this there may be minor risks, such as some bruising from the i.v. I understand that an experienced nurse or technologist will be watching for any of these problems which happen very rarely. It has been explained to me that there are also risks associated with the radioactivity in the injection. The total amount of radioactivity I will be exposed to in this procedure is approximately equal to the radiation received during a CAT-scan of the brain, which is a medical procedure that uses X-rays to make a 3-dimensional image of the head.

The purpose of this research is to study the way in which autistic adults recognize emotion. I understand that I will not benefit directly form the study in any way. I understand that I may withdraw from the study at any time. Any information collected about me during the study will be kept confidential and if the results are published, I will not be identified in any way. If I have general questions about the study, or would like to see the results of the study, I can contact Dr. Nahmias at (905) 521-2100 ext. 5667 at any time. I have read the above information and have been given the opportunity to ask further questions about the study. The study has been explained to me and my questions answered by _____.

| Name of Patient | Signature | Date |

| Name of Witness | Signature | Date |

| Name of Investigator | Signature | Date |

| Second Health Care Professional | Signature | Date |

Appendix B   Participant Recruitment Pamphlet

If you are interested please contact:

Geoff Hall

McMaster University - 521-2100 ext. 3539

The PET Scanner

The
Autism
Positron
Tomography
Study

Appendix C   Computer Programs Written in MEL*
for Facial Emotion Recognition (Study I)
and Cross-modal Emotion Recognition (Study II)

Study I - Facial Emotion Recognition Program

```
emotl.frm

03-21-01
04:28:36
EXPERIMENT emotl By: Geoff Hall 11-04-97
| code #1; initialize
```

NAMES OF: BLOCK INDEPENDENT VARS. 1:	2:	3:	4:
{to be logged for later analysis} 5:	6:	7:	8:
BLOCK DEPENDENT VARIABLES 1:	2:	3:	4:
{logs as ACcuracy,SElection, RT} 5:	6:	7:	8:
TRIAL INDEPENDENT VARIABLES 1:	2:	3:	4:
{to be logged for later analysis} 5:	6:	7:	8:
TRIAL DEPENDENT VARIABLES 1:	2:	3:	4:
{logs as ACcuracy,SElection, RT} 5:	6:	7:	8:

```
EVENT   TYPE  FORM ID      COMMENT          MISC. INSERT EXEMPLAR FIELD
   1    code      1        initialize
```

```
constant(
init = "255-60-1",
goodbye = "255-60-2",
instructions = "255-60-3",
do_blocks = "255-60-10",
do_trials = "255-60-12",
)
string(spckey(1))
integer(it)
integer(va)
string(ok(2),file(3))
string(instr(180))
integer(rec)
integer(c,xloc,yloc,rsize)
integer(block,trial,ii,delay,resp_key,target)

array_of_string(
blk_params(20,160),
trl_params(20,10),
)
```

*(Psychology Software Tools, Pittsburgh, PA)

```
BLOCK_VAR(
faceset(0,20),
)

TRIAL_VAR(
loc(0,10),
facefile(1,50),
emotion(1,20),
resprt(0,32767),
respac(0,10),
respse(0,10),
)


:255-60-1/ !=================== init ============================
!initialize stuff
graphics_on('ve:31')
create_bmap(1)
create_bmap(2)
mouse_on('m:1')
mouse_target(1,0,0,640,480)
color_clear('')
perform(do_blocks)


:255-60-2/ !=================== goodbye ==========================

color_clear('')
graphics_fore_color(215)
display_off
graphics_display(100,240,"Thank you for your participation!")
wait_top
display_on
wait(5000)
display_off
mouse_off
graphics_off


:255-60-3/ !=================== instructions =====================
display_off
color_clear('+15-0')
graphics_font('fgs-22.fnt')
graphics_fore_color(9)
set_palette_vga(9,63,63,63)
case faceset
    when 1 do begin
    graphics_display(150,100,"Match the feelings    (emotions)")
    !graphics_display(200,120,"the emotion seen in the bottom picture.")
    !graphics_display(200,300,"Press the spacebar to begin...")
    end
    when 2 do begin
    graphics_display(150,100,"Match the same person   (identity)")
    !graphics_display(200,300,"Press the spacebar to begin...")
    end
    when 3 do begin
    graphics_display(200,100,"Choose the face")
    !graphics_display(200,300,"Press the spacebar to begin...")
    end
    when 4 do begin
    graphics_display(150,100,"Match the feelings     (emotions)")
```

```
        !graphics_display(200,300,"Press the spacebar to begin...")
        end
        when 5 do begin
        graphics_display(150,100,"Match the same person   (identity)")
        !graphics_display(200,300,"Press the spacebar to begin...")
        end
        when 6 do begin
        graphics_display(200,100,"Choose the face")
        !graphics_display(200,300,"Press the spacebar to begin...")
        end
        when 7 do begin
        graphics_display(150,100,"Match the feelings    (emotions)")
        end
        when 8 do begin
        graphics_display(150,100,"Match the same person   (identity)")
        !graphics_display(200,300,"Press the spacebar to begin...")
        end
        when 9 do begin
        graphics_display(200,100,"Choose the face")
        !graphics_display(200,300,"Press the spacebar to begin...")
        end
wait_top
display_on
!mouse_target(1,0,0,640,480)
mouse_in(resp_key,target,'L','w')
key_in(spckey,' ','W',0,0)
wait(-1)
execute


:255-60-10/ !==================== do_blocks ============================

for block = 1 to 9 do begin
divide_inserts(blk_params,specific_stimulus(1,block))
faceset = number(blk_params[2])
file = blk_params[3]
instr = blk_params[4]
display_off
color_clear('+15-0')
key_in(spckey, ' ','W',0,0)
wait(-1)
execute
perform(instructions)
perform(do_trials)
log_block
end ! block
perform(goodbye)


:255-60-12/ !==================== do_trials ============================

for trial = 1 to 36 do begin
divide_inserts(trl_params,random_stimulus(2,ii))
loc = number(trl_params[1])
facefile = number(trl_params[2])
emotion = number(trl_params[3])
execute

display_off
color_clear('')
graphics_fore_color(215)
set_palette_vga(1,7,7,7)
```

```
GRAPHICS_DISPLAY( 300, 240, '+' )
wait_top
display_on
wait(500)
execute

display_off
color_clear('')
ok = string_of(facefile)
graphics_fore_color(10)
read_pcx_file('c:\mel2\pics\'+file+ok+'.pcx',1,2,0,0)
copy_bmap(1)
wait_top
display_on
mouse_target(1,0,0,640,480)
latency(resprt)
wait(100)
mouse_in(resp_key,target,'LR','w')
wait(4000)
execute
graphics_fore_color(215)
!set_palette_vga(2,63,63,63)
yloc=211
if resp_key = 1 then begin
     xloc = 150
     respse = 1
     !read_pcx_file('c:\mel2\pics\star.pcx',1,2,xloc,yloc)
     !copy_bmap(1)
     graphics_display(xloc,yloc,"*")
     end
else if resp_key = 2 then begin
     xloc = 430
     respse = 2
     graphics_display(xloc,yloc,"*")
     end
else begin
     xloc = 133
     yloc = 235
     respse = 0
     respac = 0
     graphics_display(xloc,yloc,"please press just one button - not both")
     end
!read_pcx_file('c:\mel2\star.pcx',2,2,xloc,yloc)
!copy_bmap(2)

if resprt > 0 then begin
     if resprt < 4000 then delay = 4000 - resprt
     wait(delay)
     end
wait_top
display_off
wait(500)

if (resp_key = 1 and loc = 1)
     OR (resp_key = 2 and loc = 2)
     then respac = 1 else respac = 0

log_trial
end ! trial
```

```
$ 1 CategoryName !============== INSERT CATEGORY =============================
! block categories, faceset
"1\1\a_\For this set of trials please choose which of the top two faces
    matches the emotion seen in the bottom picture.."
"2\2\ia_\For this set of trials please choose which of the top two faces
    matches the identity of the person seen in the bottom picture."
"3\3\ca_\For this set of trials please choose which of the top two boxes
    contains a face."
"4\4\b_\For this set of trials please choose which of the top two faces
    matches the emotion seen in the bottom picture."
"5\5\ib_\For this set of trials please choose which of the top two faces
    matches the identity of the person seen in the bottom picture."
"6\6\cb_\For this set of trials please choose which of the top two boxes
    contains a face."
"7\7\c_\For this set of trials please choose which of the top two faces
    matches the emotion seen in the bottom picture."
"8\8\ic_\For this set of trials please choose which of the top two faces
    matches the identity of the person seen in the bottom picture."
"9\9\cc_\For this set of trials please choose which of the top two boxes
    contains a face."


$ 2 CategoryName !=============== INSERT CATEGORY ============================
1\1\1 !happy, id, detect variables
2\2\1 !happy
1\3\1 !happy
2\4\1 !happy
1\5\1 !happy
2\6\1 !happy
1\7\2 !sad
2\8\2 !sad
1\9\2 !sad
2\10\2 !sad
1\11\2 !sad
2\12\2 !sad
1\13\3 !fear
2\14\3 !fear
1\15\3 !fear
2\16\3 !fear
1\17\3 !fear
2\18\3 !fear
1\19\4 !anger
2\20\4 !anger
1\21\4 !anger
2\22\4 !anger
1\23\4 !anger
2\24\4 !anger
1\25\5 !disgust
2\26\5 !disgust
1\27\5 !disgust
2\28\5 !disgust
1\29\5 !disgust
2\30\5 !disgust
1\31\6 !surprise
2\32\6 !surprise
1\33\6 !surprise
2\34\6 !surprise
```

1\35\6 !surprise
2\36\6 !surprise

DEFAULT SPECIFICATION # 1   c:\mel2\emot1

Collect subject information for data logging yes
Path to Setup,Run,Makedat,Analyze \mel2
Does your screen flicker on displays (IBM CGA video adaptor) no
Independent variables Minimum 0   Maximum 40
Maximum value for dependent variable RT 32767 Maximum value for QANSWER 40

Insert Type:	Block	Trial/Question/Text	Frame	User	Subject	Misc
# of slots	10	10	10	10	5	5
# chars/slot	800	80	80	80	15	15

Length of tone for incorrect responses 500   Length of feedback display 500
Generate as an INCLUDE file no   Run file name run.exe
Clear on feedback yes   At frame execution set CapsLock low and NumLock num
Time resolution 1   Run limit inserts no
Counter balance none   Balance category number 255
Graphics mode ''   Warn on duration not multiple of refresh time yes
Auto answer no   Subject init options #s
Overlay FORM with RUN yes Max questions allowed per questionnaire 100
Minimum value for QANSWER 0
End report log Wait type exclude Sound device speaker
Response box: Model   Port   Init options
Random seed 0   Run-time retrace verification fatal Time audit off

---

Study II - Cross-modal Emotion Matching Program

crossa.frm

03-21-01
04:30:12
EXPERIMENT crossa By: Geoff Hall 08-14-99
| code #1; initialize

                    Forms Not Explicitly Referenced
CODE #2
CODE #3
CODE #10
CODE #12
INSERT #1
INSERT #2

                        EXPERIMENT SPECIFICATION # 1   c:\mel2\crossa
AUTHOR Geoff Hall   CREATION DATE 09-18-97 LAST UPDATE 08-14-99
FILES: EXP crossa   DATA crossa   INSERT crossa   INCLUDE
BACKUP DISK VOLUME   DEBUG normal   SPARE
ABSTRACT

NAMES OF: BLOCK INDEPENDENT VARS   1:   2:   3:   4:
  {to be logged for later analysis} 5:   6:   7:   8:
          BLOCK DEPENDENT VARIABLES 1:   2:   3:   4:
  {logs as ACcuracy,SElection, RT} 5:   6:   7:   8:
        TRIAL INDEPENDENT VARIABLES 1:   2:   3:   4:
  {to be logged for later analysis} 5:   6:   ' 7:   8:
        TRIAL DEPENDENT VARIABLES   1:   2:   3:   4:
  {logs as ACcuracy,SElection, RT} 5:   6:   7:   8:
EVENT   TYPE   FORM ID   COMMENT   MISC. INSERT EXEMPLAR FIELD
   1 code   1   initialize


```
constant(
init = "255-60-1",
goodbye = "255-60-2",
instructions = "255-60-3",
do_blocks = "255-60-10",
do_trials = "255-60-12",
num_files=3)

string(spckey(1))
integer(it)
integer(va)
string(ok(2),file(3))
string(instr(180))
integer(rec)
integer(c,xloc,yloc,rsize)
integer(block,trial,ii,delay,resp_key,target)
string(response(num_files))
integer(trial_buffer,bits_per_sample,num_channels,reference,i)
real(duration,sample_rate,buffer_size)
```

```
array_of_string(
blk_params(20,160),
trl_params(20,10),
)

BLOCK_VAR(
faceset(0,20),
)

TRIAL_VAR(
loc(0,10),
facefile(1,50),
emotion(1,20),
resprt(0,32767),
respac(0,10),
respse(0,10),
)

:255-60-1/ !==================== init ============================
!initialize stuff
graphics_on('ve:31')
create_bmap(1)
create_bmap(2)
mouse_on('m:2')
mouse_target(1,0,0,640,480)
color_clear('')
perform(do_blocks)

:255-60-2/ !==================== goodbye ==========================

color_clear('')
graphics_fore_color(215)
display_off
graphics_display(100,240,"Thank you for your participation!")
wait_top
display_on
wait(5000)
display_off
mouse_off
graphics_off

:255-60-3/ !==================== instructions =======================
display_off
color_clear('+15-0')
graphics_font('fgs-22.fnt')
graphics_fore_color(9)
set_palette_vga(9,63,63,63)
case faceset
    when 1 do begin
    graphics_display(100,100,"Match the face to the vocal emotion")
    !graphics_display(200,300,"Press the spacebar to begin...")
    end
    when 2 do begin
    graphics_display(100,100,"Match the voice to the gender")
    graphics_display(200,320,"(male or female)")
    !graphics_display(200,300,"Press the spacebar to begin...")
    end
    when 3 do begin
    graphics_display(100,100,"Match the face to the vocal emotion")
    !graphics_display(200,300,"Press the spacebar to begin...")
```

```
                  end
                  when 4 do begin
                  graphics_display(100,100,"Match the voice to the gender")
                  !graphics_display(200,300,"Press the spacebar to begin...")
                  end
                  when 5 do begin
                  graphics_display(100,100,"Match the face to the vocal emotion")
                  !graphics_display(200,300,"Press the spacebar to begin...")
                  end
                  when 6 do begin
                  graphics_display(200,100,"Match the voice to the gender")
                  !graphics_display(200,300,"Press the spacebar to begin...")
                  end
                  when 7 do begin
                  graphics_display(100,100,"Match the face to the vocal emotion")
                  !graphics_display(200,300,"Press the spacebar to begin...")
                  end
                  when 8 do begin
                  graphics_display(150,100,"Match the voice to the gender")
                  !graphics_display(200,300,"Press the spacebar to begin...")
                  end
                  when 9 do begin
                  graphics_display(100,100,"Match the face to the vocal emotion")
                  !graphics_display(200,300,"Press the spacebar to begin...")
                  end
          wait_top
          display_on
          mouse_in(resp_key,target,'L','w')
          key_in(spckey, ' ','W',0,0)
          wait(-1)
          execute

          :255-60-10/ !===================== do_blocks =============================
          AUDIO_INIT('B1')

          for block = 1 to 8 do begin

          divide_inserts(blk_params,specific_stimulus(1,block))
          faceset = number(blk_params[2])
          file = blk_params[3]
          instr = blk_params[4]
          display_off
          color_clear('+15-0')
          key_in(spckey, ' ','W',0,0)
          wait(-1)
          execute
          perform(instructions)
          perform(do_trials)
          log_block
          end ! block
          perform(goodbye)

          :255-60-12/ !===================== do_trials =======================

          for trial = 1 to 36 do begin

          divide_inserts(trl_params,random_stimulus(2,ii))
          loc = number(trl_params[1])
          facefile = number(trl_params[2])
```

```
emotion = number(trl_params[3])
execute


ok = string_of(facefile)

AUDIO_GET_FILEFORMAT('c:\mel2\cross\wav\'+ file + ok +'.wav',
num_channels, bits_per_sample, sample_rate, duration)
buffer_size =
(FLOAT(num_channels)*FLOAT(bits_per_sample/8)*
(duration/1000.0)*sample_rate/1024.0)
trial_buffer=AUDIO_CREATE_BUFFER(TRUNC(buffer_size)+1)
AUDIO_SET_BUFFERFORMAT(trial_buffer, num_channels, bits_per_sample,
sample_rate)
AUDIO_SETPOS_MSECS(trial_buffer,2,0.0)
AUDIO_READ_FILE('c:\mel2\cross\wav\'+ file + ok + '.wav',trial_buffer,TRUE)
AUDIO_SETPOS_MSECS(trial_buffer,0,0.0)
execute

display_off
color_clear('')
graphics_fore_color(215)
set_palette_vga(1,7,7,7)
GRAPHICS_DISPLAY( 300, 300, '+' )
wait_top
display_on
wait(600)
execute

display_off
color_clear('')
ok = string_of(facefile)
graphics_fore_color(10)
read_pcx_file('c:\mel2\cross\'+file+ok+'.pcx',1,2,0,0)
copy_bmap(1)
wait_top
display_on
mouse_target(1,0,0,640,480)

latency(resprt)
AUDIO_PLAY(trial_buffer,'')
!WAIT(600)

mouse_in(resp_key,target,'LR','w')
wait(3200)
execute
graphics_fore_color(215)
!set_palette_vga(2,63,63,63)
yloc=421


AUDIO_DESTROY_BUFFER(trial_buffer)
execute
if resp_key = 1 then begin
    xloc = 455
    respse = 1
    !read_pcx_file('c:\mel2\cross\star.pcx',1,2,xloc,yloc)
    !copy_bmap(1)
    graphics_display(xloc,yloc,"*")
    end
```

```
      else if resp_key = 2 then begin
          xloc = 160
          respse = 2
          graphics_display(xloc,yloc,"**")
          end
      else if resp_key = 3 then begin
          graphics_display(133,455,"please press just one button - not both")
          respse = 0
          respac = 0
          end

      else begin
          xloc = 133
          yloc = 455
          respse = 0
          respac = 0
          end


      if resprt > 0 then begin
          wait(800)
          display_off
          if resprt < 2400 then delay = 2400 - resprt
          wait(delay)
          end
      !wait_top
      !display_off
      !wait(300)

      if (resp_key = 1 and loc = 1)
          OR (resp_key = 2 and loc = 2)
          then respac = 1 else respac = 0

      log_trial
      end ! trial




$ 1 CategoryName !================ INSERT CATEGORY ==============================
! block categories, faceset
"1\1\ca_\For this set of trials please choose which of the top two faces
    matches the emotion seen in the bottom picture."
"2\2\ba_\For this set of trials please choose which of the top two faces
    matches the identity of the person seen in the bottom picture."
"3\3\cb_\For this set of trials please choose which of the top two boxes
    contains a face."
"4\4\bb_\For this set of trials please choose which of the top two faces
    matches the emotion seen in the bottom picture."
"5\5\cc_\For this set of trials please choose which of the top two faces
    matches the identity of the person seen in the bottom picture."
"6\6\bc_\For this set of trials please choose which of the top two boxes
    contains a face."
"7\7\cd_\For this set of trials please choose which of the top two faces
    matches the emotion seen in the bottom picture."
"7\8\bd_\For this set of trials please choose which of the top two faces
    matches the identity of the person seen in the bottom picture."
```

```
$ 2 CategoryName !=============== INSERT CATEGORY ===============================
1\1\1  !happy, id, detect variables
2\2\1  !happy male
1\3\1  !happy male
2\4\1  !happy male
1\5\9  !happy male/female
2\6\2  !happy female
1\7\2  !happy female
2\8\2  !happy female
1\9\2  !happy female
2\10\3 !sad male
1\11\3 !sad male
2\12\3 !sad male
1\13\3 !sad male
2\14\9 !sad male/female
1\15\4 !sad female
2\16\4 !sad female
1\17\4 !sad female
2\18\4 !sad female
1\19\5 !angry male
2\20\5 !angry male
1\21\5 !angry male
2\22\5 !angry male
1\23\9 !angry female/female
2\24\6 !angry female
1\25\6 !angry female
2\26\6 !angry female
1\27\6 !angry female
2\28\7 !surprise male
1\29\7 !surprise male
2\30\7 !surprise male
1\31\7 !surprise male
2\32\9 !surprise male/female
1\33\8 !surprise female
2\34\8 !surprise female
1\35\8 !surprise female
2\36\8 !surprise female
```

```
                        DEFAULT SPECIFICATION  # 1   c:\mel2\crossa
Collect subject information for data logging yes
Path to Setup,Run,Makedat,Analyze \mel2
Does your screen flicker on displays (IBM CGA video adaptor) no
Independent variables Minimum 0      Maximum 40
Maximum value for dependent variable RT 32767 Maximum value for QANSWER 40
Insert Type:  Block  Trial/Question/Text  Frame    User    Subject  Misc
# of slots    10         10               10       10      5        5
# chars/slot  800        80               80       80      15       15
Length of tone for incorrect responses 500   Length of feedback display 500
Generate as an INCLUDE file no              Run file name run.exe
Clear on feedback yes    At frame execution set CapsLock low and NumLock num
Time resolution 1        Run limit inserts no
Counter balance none     Balance category number 255
Graphics mode ''         Warn on duration not multiple of refresh time yes
Auto answer no           Subject init options #s
Overlay FORM with RUN yes  Max questions allowed per questionnaire 100
Minimum value for QANSWER 0

End report log  Wait type exclude  Sound device speaker
Response box: Model       Port         Init options
Random seed 0        Run-time retrace verification fatal  Time audit off
```

Appendix D   Repeated Measures Analyses of Variance
Response Latency and Error Data

GLM REPEATED MEASURES

WITHIN Ss FACTORS = Blocks & Trials

BETWEEN Ss FACTORS = Groups

TEST OF WITHIN Ss EFFECTS
    asks are there differences across the blocks or trials
    Gives the significance level of repeated measures factors and the
    BLOCK X TRIAL AND
    TRIAL X GROUP interactions

TEST OF BETWEEN Ss EFFECTS
    Gives the significance level of the between Ss factor (Group)

Study I   Repeated Measures Anova #1:
Response Latencies to Detection Trials

Within Ss Factors = Blocks X 3 & Trials x 36
Between Ss Factors = Group (M or F)

Mauchly - Blocks is Not Significant   Block = .105
∴ homogeneity of variance is assumed. Sphericity is assumed

Test of Within Subjects Effects

Block	$F_{(2, 28)} = 12.174$	P = 0.000
Trials	$F_{(35, 490)} = 0.942$	P = 0.567
Block X Group	$F_{(2, 28)} = 0.001$	P = 0.999
Trials X Group	$F_{(35, 490)} = 0.799$	P = 0.386
Block X Trials	$F_{(70, 980)} = 1.099$	p = 0.276
Block X Trials X Group	$F_{(70, 980)} = 1.446$	P = 0.011

Between Ss Effects
Group $F_{(1, 14)} = 0.030$ P = 0.864

Study I   Repeated Measures Anova #2:   Errors on Detection Trials

Within Ss Factors = Blocks X 3 & Trials x 36
Between Ss Factors = Group (M or F)

Mauchly - Blocks is Significant   Block = 0.054
∴ homogeneity of variance cannot be assumed. - Adjustments must be made to degrees of freedom- Greenhouse-Geiser values reported below

Test of Within Subjects Effects

Block	$F_{(2, 28)} = .993$	P = 0.382
Trials	$F_{(35, 490)} = 1.423$	P = 0.253
Block X Group	$F_{(2, 28)} = 0.000$	P = 1.000
Trials X Group	$F_{(35, 490)} = 0.512$	P = 0.651
Block X Trials	$F_{(70, 980)} = 1.517$	p = 0.229
Block X Trials X Group	$F_{(70, 980)} = 0.515$	P = 0.652

Between Ss Effects
Group $F_{(1, 14)} = 0.000$ P = 1.000

Study I   Repeated Measures Anova #3   Response Latencies to Identity Trials

Within Ss Factors = Blocks X 3 & Trials x 36
Between Ss Factors = Group (M or F)

Mauchly - Blocks is Not Significant   Block = .670
∴ homogeneity of variance is assumed. Sphericity is assumed

Test of Within Subjects Effects

Block	$F_{(2, 28)} = 7.547$	P = 0.002
Trials	$F_{(35, 490)} = 5.606$	P = 0.000
Block X Group	$F_{(2, 28)} = 0.080$	P = 0.924
Trials X Group	$F_{(35, 490)} = 1.012$	P = 0.452
Block X Trials	$F_{(70, 980)} = 6.682$	p = 0.000
Block X Trials X Group	$F_{(70, 980)} = 0.826$	P = 0.843

Between Ss Effects
Group $F_{(1, 14)} = 0.122$ P = 0.732

Study I   Repeated Measures Anova #4   Errors on Identity Trials

Within Ss Factors = Blocks X 3 & Trials x 36
Between Ss Factors = Group (M or F)

Mauchly - Blocks is Significant   Block = 0.016
∴ homogeneity of variance cannot be assumed. - Adjustments must be made to degrees of freedom- Greenhouse-Geiser values reported below

Test of Within Subjects Effects

Block	$F_{(2, 28)} = 6.142$	P = 0.016
Trials	$F_{(35, 490)} = 14.841$	P = 0.000
Block X Group	$F_{(2, 28)} = 2.047$	P = 0.166
Trials X Group	$F_{(35, 490)} = 1.309$	P = 0.263
Block X Trials	$F_{(70, 980)} = 13.168$	p = 0.000
Block X Trials X Group	$F_{(70, 980)} = 1.118$	P = 0.359

Between Ss Effects
Group $F_{(1, 14)} = 2.386$ P = 0.145

Study I   Repeated Measures Anova #5:   Response Latencies to Emotion Trials

Within Ss Factors = Blocks X 3 & Trials x 36
Between Ss Factors = Group (M or F)

Mauchly - Blocks is Not Significant ∴ homogeneity of variance is assumed. Sphericity is assumed

Test of Within Subjects Effects

Block	$F_{(2, 28)} = 5.348$	$P = 0.011$
Trials	$F_{(35, 490)} = 13.746$	$P = 0.000$
Block X Group	$F_{(2, 28)} = 0.403$	$P = 0.672$
Trials X Group	$F_{(35, 490)} = 0.731$	$P = 0.872$
Block X Trials	$F_{(70, 980)} = 3.840$	$p = 0.000$
Block X Trials X Group	$F_{(70, 980)} = 0.881$	$P = 0.746$

Between Ss Effects
Group $F_{(1,14)} = 1.085$ $P = 0.315$

Study I   Repeated Measures Anova #7: Errors on Emotion Trials

3 Blocks X 6 Trials per emotion
Between Ss Factor = Group
Mauchly   Block = .353 ~NS   ∴ Sphericity Assumed

Tests of Within Ss

Block	$F_{(2, 28)} = 7.968$	$P = 0.002$
Trials	$F_{(35, 490)} = 8.428$	$P = 0.000$
Block X Group	$F_{(2, 28)} = 0.757$	$P = 0.478$
Trials X Group	$F_{(35, 490)} = 1.137$	$P = 0.349$
Block X Trials	$F_{(70, 980)} = 7.980$	$P = 0.000$
Block X Trials X Group	$F_{(70, 980)} = 0.668$	$P = 0.752$

Between Ss Effects
Group $F_{(1,14)} = 0.951$ $P = 0.346$

Study II   Repeated Measures Anova #1:
Male / Female Response Latencies to Gender Trials

Within Ss Factors = 4 Blocks X 36 Trials
Between Ss Factors = Group (male or female)

Mauchly - Blocks is Not Significant   Block = .285 (generally 0.05 used as set point)
∴ homogeneity of variance is assumed. Sphericity is assumed

Test of Within Subjects Effects

Block	$F(3, 27) = 3.624$	$P = 0.027$
Trials	$F(35, 315) = 3.790$	$P = 0.000$
Block X Group	$F(3, 27) = 3.214$	$P = 0.041$
Trials X Group	$F(35, 315) = 1.365$	$P = 0.090$
Block X Trials	$F(105, 945) = 1.059$	$p = 0.332$
Block X Trials X Group	$F(105, 945) = 1.311$	$P = 0.025$

Between Ss Effects
Group $F(1, 9) = 0.068$ $P = 0.800$

Study II   Repeated Measures Anova #2:
Males / Females   Errors to Gender Trials

Within Ss Factors = 4 Blocks X 36 Trials
Between Ss Factors = Group (male or female)

Mauchly - Blocks is Significant   Block = .004 (generally 0.05 used as set point)
∴ homogeneity of variance is not assumed. Greenhouse Geisser results reported.

Test of Within Subjects Effects

Block	$F(3, 27) = 0.505$	$P = 0.541$
Trials	$F(35, 315) = 0.889$	$P = 0.475$
Block X Group	$F(3, 27) = 0.849$	$P = 0.408$
Trials X Group	$F(35, 315) = 0.911$	$P = 0.464$
Block X Trials	$F(105, 945) = 1.059$	$p = 0.332$
Block X Trials X Group	$F(105, 945) = 0.943$	$P = 0.448$

Between Ss Effects
Group $F(1, 9) = 0.379$ $P = 0.555$

Study II   Repeated Measures Anova #3:
Male / Female Response Latencies to Emotion Trials

Within Ss Factors = 4 Blocks X 36 Trials
Between Ss Factors = Group (male or female)
Mauchly - Blocks is Not Significant   Block = .919   (generally 0.05 used as set point)
∴ homogeneity of variance is assumed. Sphericity is assumed

Test of Within Subjects Effects

Block	$F(3, 27) = 15.091$	$P = 0.000$	
Trials	$F(35, 315)= 4.835$	$P = 0.000$	
Block X Group	$F(3, 27) = 11.409$	$P = 0.000$	
Trials X Group	$F(35, 315) = 1.543$	$P = 0.030$	
Block X Trials	$F(105, 945) = 1.400$	$p = 0.007$	
Block X Trials X Group	$F(105, 945) = 0.946$		$P = 0.634$

Between Ss Effects
Group $F(1, 9) = 0.000$ $P = 0.992$

Study II   Repeated Measures Anova #4:
Male / Female   Errors to Emotion Trials

Within Ss Factors = 4 Blocks X 36 Trials
Between Ss Factors = Group (male or female)

Mauchly - Blocks is Not Significant   Block = .06 (generally 0.05 used as set point)
∴ homogeneity of variance is assumed. Sphericity is assumed

Test of Within Subjects Effects

Block	$F(3, 27) = 11.650$	$P = 0.000$	
Trials	$F(35, 315) = 1.154$	$P = 0.260$	
Block X Group	$F(3, 27) = 0.352$	$P = 0.788$	
Trials X Group	$F(35, 315) = 1.628$	$P = 0.017$	
Block X Trials	$F(105, 945) = 1.233$	$p = 0.064$	
Block X Trials X Group	$F(105, 945) = 1.195$	$P = 0.099$	

Between Ss Effects
Group $F(1, 9) = 0.009$ $P = 0.926$

Study II   Repeated Measures Anova #5:
Autism / Control Response Latencies to Gender Trials

Within Ss Factors = 4 Blocks X 36 Trials
Between Ss Factors = Group (Autism or Control)

Mauchly - Blocks is Not Significant   Block = .878 (generally 0.05 used as set point)
∴ homogeneity of variance is assumed. Sphericity is assumed

Test of Within Subjects Effects

Block $F(3, 33)= 2.814$ P = 0.058
Trials $F(35, 385)= 4.751$ P = 0.000
Block X Group $F(3, 33)= 2.922$ P = 0.052
Trials X Group $F(35, 385)= 1.022$ P = 0.438
Block X Trials $F(105, 1155) = 2.172$ p = 0.000
Block X Trials X Group $F(105, 1155) = 1.138$ P = 0.172

Between Ss Effects
Group $F(1, 11) = 0.428$ P = 0.529

Study II   Repeated Measures Anova #6:
Autism / Control   Errors to Gender Trials

Within Ss Factors = 4 Blocks X 36 Trials
Between Ss Factors = Group (Autism or Control)

Mauchly - Blocks is Significant   Block = .001 (generally 0.05 used as set point)
∴ homogeneity of variance is not assumed. Greenhouse Geisser results reported.

Test of Within Subjects Effects

Block $F(3, 33) = 1.494$ P = 0.252
Trials $F(35, 385) = 1.377$ P = 0.259
Block X Group $F(3, 33) = 0.143$ P = 0.775
Trials X Group $F(35, 385) = 1.864$ P = 0.135
Block X Trials $F(105, 1155) = 0.848$ p = 0.859
Block X Trials X Group $F(105, 1155) = 0.920$ P = 0.472

Between Ss Effects
Group $F(1, 11) = 2.708$ P = 0.131

Study II   Repeated Measures Anova #7:
Autism / Control Response Latencies to Emotion Trials

Within Ss Factors = 4 Blocks X 36 Trials
Between Ss Factors = Group (Autism or Control)

Mauchly - Blocks is Not Significant   Block = .079 (generally 0.05 used as set point)
∴ homogeneity of variance is assumed. Sphericity is assumed

Test of Within Subjects Effects

Block $F_{(3, 33)} = 2.590$ $P = 0.069$
Trials $F_{(35, 385)} = 3.451$ $P = 0.000$
Block X Group $F_{(3, 33)} = 2.451$ $P = 0.081$
Trials X Group $F_{(35, 385)} = 0.668$ $P = 0.928$
Block X Trials $F_{(105, 1155)} = 1.695$ $p = 0.000$
Block X Trials X Group $F_{(105, 1155)} = 0.960$ $P = 0.595$

Between Ss Effects
Group $F_{(1, 11)} = 0.027$ $P = 0.872$

Study II   Repeated Measures Anova #8:
Autism / Control   Errors to Emotion Trials

Within Ss Factors = 4 Blocks X 36 Trials
Between Ss Factors = Group (Autism or Control)

Mauchly - Blocks is Not Significant   Block = .426 (generally 0.05 used as set point)
∴ homogeneity of variance is assumed. Sphericity is assumed

Test of Within Subjects Effects

Block $F_{(3, 33)} = 6.729$ $P = 0.001$
Trials $F_{(35, 385)} = 1.373$ $P = 0.082$
Block X Group $F_{(3, 33)} = 2.984$ $P = 0.045$
Trials X Group $F_{(35, 385)} = 1.367$ $P = 0.085$
Block X Trials $F_{(105, 1155)} = 1.291$ $p = 0.031$
Block X Trials X Group $F_{(105, 1155)} = .859$ $P = 0.839$

Between Ss Effects
Group $F_{(1, 11)} = 10.422$ $P = 0.008$

Bibliography

Abell, F., Krams, M., Ashburner, J., Passingham, R., Friston, K., Frackowiak, R., Happe, F., Frith, C. & Frith, U. (1999). The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. NeuroReport, 10: 1647 - 1651.

Aboitiz, F., Scheibel, A.B., Fisher, R.S. & Zaidel, E. (1992). Fiber composition of human corpus callosum. Brain Research, 598: 143 - 153.

Adolphs, R. Tranel, D., Damasio, H. & Damasio, A.R. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature, 372: 669 - 672.

Adolphs, R., Damasio, H., Tranel, D. & Damasio, A.R. (1996). Cortical systems for the recognition of emotion in facial expressions. The Journal of Neuroscience, 16: 7678 - 7687.

Aggleton, J.P. (1993). The contribution of the amygdala to normal and abnormal emotional states. Trends in Neurosciences, 16: 328 - 333.

Allen, J.G. & Haccoun, D.M. (1976). Sex differences in emotionality: A multidimensional approach. Human Relations, 29: 711 - 722.

Allison, T., McCarthy, G., Nobre, A., Puce, A., & Belger, A. (1994). Human extrastriate visual cortex and the perception of faces, words, and colors. Cerebral Cortex, 5: 544 - 554.

American Psychiatric Association. (1994). Diagnostic and Statistical Manual of Mental Disorders (4th ed.). Author : Washington, D.C.

Anderson, A.K. & Phelps, E.A. (1998). Intact recognition of vocal expressions of fear following bilateral lesions of the human amygdala. Neuroreport, 16: 3607 - 3613.

Andreasen, N.C., O'Leary, D.S., Arndt, S., Cizadlo, T., Hurtig, R., Rezai, K., Watkins, G.L., Ponto, L.B. & Hichwa, R.D. (1996). Neural substrates of facial recognition. Journal of Neuropsychiatry and Clinical Neuroscience, 8: 139 - 146.

Andreoli J., Rodier P. & Langman J. (1973). The influence of a prenatal trauma on formation of Purkinje cells. American Journal of Anatomy, 137: 87 - 101.

Arndt, S., Cizadlo, T., Andreasen, N.C., Zeien, G., Harris, G., O'Leary, D.S., Watkins, G.L., Ponto, L.L. & Hichwa, R.D. (1995). A comparison of approaches to the statistical analysis of [15O]H2O PET cognitive activation studies. Journal of Neuropsychiatry and Clinical Neuroscience, 7: 155 - 168.

Arndt, S., Cizadlo, T., Andreasen, N.C., Heckel, D., Gold, S. & O'Leary, D.S. (1996). Tests for comparing images based on randomization and permutation methods. Journal of Cerebral Blood Flow Metabolism, 16: 1271 - 1279.

Asthana, H.S. & Mandal, M.K. (1998). Hemifacial asymmetry in emotion expressions. Behavior Modification, 22: 177 - 183.

Astington, J.W. (1988). Children's understanding of the speech act of promising. Journal of Child Language, 15: 157 - 173.

Aylward, E.H., Minshew, N.J., Goldstein, G., Honeycutt, N.A., Augustine, A.M., Yates, K.O., Barta, P.E., & Pearlson, G.D. (1999). MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. Neurology, 53: 2145 - 2150.

Bachevalier, J. & Merjanian, P.M. (1994). The contribution of medial temporal lobe structures in infantile autism: A neurobehavioral study in primates. In: The Neurobiology of Autism. M.L. Bauman & T.L. Kemper (Eds.). Johns Hopkins University Press, London.

Bailey, A., Le Couteur, A., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E. & Rutter, M. (1995). Autism as a strongly genetic disorder: Evidence from a British twin study. Psychological Medicine, 25: 63 - 77.

Baranek, G.T. (1999). Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9 - 12 months of age. Journal of Autism and Developmental Disorders, 29: 213 - 224.

Barbas, H. (1995). Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. Neuroscience and Biobehavioral Reviews, 19: 499 -510.

Baron, J.C., Lebrun-Grandie, P., Collard, P., Crouzel, C., Mestelan, G. & Bousser, M.G. (1982). Noninvasive measurement of blood flow, oxygen consumption, and glucose utilization in the same brain regions in man by positron emission tomography: concise communication. Journal of Nuclear Medicine, 23: 391 - 399.

Baron-Cohen, S. (1988). Social and pragmatic deficits in autism: cognitive or affective? Journal of Autism and Developmental Disorders, 18: 379 - 402.

Baron-Cohen, S., Leslie, A.M. & Frith, U. (1985). Does the autistic child have a 'theory of mind'? Cognition, 21: 37 - 46.

Baron-Cohen, S., Cox, A., Baird, G., Swettenham, J., Nightingale, N., Morgan, K., Drew, A. & Charman, T. (1996). Psychological markers in the detection of autism in infancy in a large population. British Journal of Psychiatry, 168: 158 - 163.

Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A. & Williams, S.C.R. (1999). Social intelligence in the normal and autistic brain: An fMRI study. European Journal of Neuroscience, 11: 1891 - 1898.

Baron-Cohen, S., Ring, H.A., Bullmore, E.T., Wheelwright, S., Ashwin, C. & Williams, S.C.R. (2000). The amygdala theory of autism. Neuroscience and Biobehavioral Reviews, 24: 355 - 364.

Barthelemy, C., Adrien, J.L., Garreau, P., & Lelord, G. (1994). Cognitive and social dysfunction in childhood autism: a neuropsychological and physiological approach. Acta Paedopsychiatrica, 56: 261 - 265.

Bates, E. Benigni, L., Bretherton, I., Camaioni, L. & Volterra, V. (1979). Cogniton and Communication from 9 to 13 months, correlational findings. In E. Bates (Ed.) The Emergence of Symbols: Cognition and Communication in Infancy, New York: Academic Press. pp. 69 - 140.

Bauer, S. (1995). Autism and the pervasive developmental disorders: Part 1. Pediatrics in Review, 16: 130 - 136.

Bauman, M.L. (1991). Microscopic neuroanatomic abnormalities in autism. Pediatrics, 87 (S): 791 - 796.

Bauman, M.L., & Kemper, T.L. (1985). Histoanatomic observations of the brain in early infantile autism. Neurology, 35: 866 - 874.

Bauman, M.L., & Kemper, T.L., (1994). Neuroanatomic observations of the brain in autism. In M.L. Bauman & T.L. Kemper (Eds.). The Neurobiology of Autism. Johns Hopkins University Press, Baltimore: 119 - 145.

Belmonte, M., Egaas, B., Townsend, J., & Courchesne, E. NMR intensity of corpus callosum differs with age but not with diagnosis of autism. NeuroReport, 6 : 1253 - 1256.

Bennetto, L., Pennington, B.F. & Rogers, S.J. (1996). Intact and impaired memory functions in autism. Child Development, 67: 1816 - 1835.

Berger, H.J., Spaendonck, K.P., Horstink, M.W., Buytenhuijs, E.L., Lammers, P.W., & Cools, A.R.(1993). Cognitive shifting as a predictor in social understanding in high functioning adolescents with autism: A prospective study. Journal of Autism and Developmental Disorders, 23: 341 - 359.

Berger-Sweeney, J. & Hohmann, C.F. (1997). Behavioral consequences of abnormal cortical development: insights into developmental disabilities. Behavioural Brain Research, 86: 121 - 142.

Beversdorf, D.Q., Anderson, J.M., Manning, S.E., Anderson, S.L., Nordgren, R.E., Felopulos, G.J., Nadeau, S.E., Heilman, K.E. & Bauman, M.L. (1998). The effect of semantic and emotional context on written recall for verbal language in high functioning adults with autism spectrum disorder. Journal of Neurology, Neurosurgery and Psychiatry, 65: 685 - 692.

Blair, R.J.R., Morris, J.S., Frith, C.D., Perrett, D.I. & Dolan, R.J. (1999). Dissociable neural responses to facial expressions of sadness and anger. Brain, 122: 883 - 893.

Borod, J.C. (1992). Interhemispheric and intrahemispheric control of emotion: A focus on unilateral brain damage. Journal of Clinical and Consulting Psychology, 60: 339 - 348.

Borod, J.C. (1993). Cerebral mechanisms underlying facial, prosodic, and lexical emotional expression: A review of neuropsychological studies and methodological issues. Neuropsychology, 7: 445 - 463.

Bowers, D., Bauer, R.M. Coslett, H.B., Heilman, K.M. (1985). Processing of faces by patients with unilateral hemisphere lesions. I. Dissociation between judgments of facial affect and facial identity. Brain and Cognition, 4: 258 - 272

Braverman, M., Fein, D., Lucci, D., & Waterhouse, L. (1989). Affect comprehension in children with pervasive developmental disorders. Journal of Autism and Developmental Disorders, 19: 301 - 315.

Brihaye, C., Depresseux, J.-C. & Comar, D. (1995). Radiation dosimetry for bolus administration of oxygen-15-water. Journal of Nuclear Medicine, 36: 651 - 656.

Bristol, M.M., Cohen, D.J., Costello, E.J., Denckla, M., Eckberg, T.J., Kallen, R., Kraemer, H.C., Lord, C., Maurer, R., McIlvane, W.J., Minshew, N., Sigman, M., Spence, M.A. (1996). State of the science in autism: Report to the National Institutes of Health. Journal of Autism and Developmental Disorders, 26: 121 - 154.

Bryson, C.Q. (1972). Short-term memory and cross-modal information processing in autistic children. Journal of Learning Disabilities, 5: 25 - 35.

Bryson, S.E. (1991). Our Most Vulnerable Citizens: Report of the Adult Task Force. Autism Society Ontario, Thornhill, Canada.

Bryson, S.E. (1996). Brief report: Epidemiology of autism. Journal of Autism and Developmental Disorders, 26: 165 - 167.

Bryson, S.E., Clark, B.S. & Smith, I.M. (1988). First report of a Canadian epidimiological study of autistic syndromes. Journal of Child Psychology and Psychiatry, 29: 433 - 446.

Buchanan, T.W., Lutz, K., Mirzazade, S., Specht, K., Shah, N.J., Zilles, K. & Jancke, L. (2000). Recognition of emotional prosody and verbal components of spoken language : an fMRI study. Cognitive Brain Research, 9: 227 - 238.

Buchel, C., Price, C., Frackowiak, R.S.J. & Friston, K. (1998). Different activation patterns in the visual cortex of late and congenitally blind subjects. Brain, 121: 409 - 419.

Buchsbaum, M.S., Siegel, B.V., Wu, J.C., Hazlett, E., Sicotte, N., Haier, R., Tanguay, P., Asarnow, R., Cadorette, T., Donoghue, D., Lagunas-Solar, M., Lott, I., Paek, J., & Sabalsesky, D. (1992) Attention performance in autism and regional brain metabolic rate assessed by positron emission tomography, Journal of Autism and Developmental Disorders, 22: 115 - 125.

Buitelaar, J.K., & Van der Wees, M. (1997). Are deficits in the decoding of affective cues and in mentalizing abilities independent? Journal of Autism and Developmental Disorders, 27, 539 - 556.

Buonocore, M.H., & Hecht, S.T. (1995). Functional magnetic resonance imaging depicts the brain in action. Nature Medicine, 1: 379 - 380.

Butler, S. (1984). Sex differences in human cerebral function. Progress in Brain Research, 61: 443 - 454.

Calvert, G.A., Brammer, M.J., Bullmore, E.T., Campbell, R., Iversen, S.D. & David, A.S. (1999). Response amplification in sensory-specific cortices during crossmodal binding. NeuroReport, 10: 2619 - 2623.

Calvert, G.A., Campbell, R. & Brammer, M.J. (2000). Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. Current Biology, 10: 649 - 657.

Capps, L., Yirmiya, N. & Sigman, M. (1992). Understanding of simple and complex emotions in non-retarded children with Autism. Journal of Child Psychology and Psychiatry, 33: 1169 - 1182.

Carper, R.A. & Courchesne, E. (2000). Inverse correlation between frontal lobe and cerebellum sizes in children with autism. Brain, 123: 836 - 844.

Casey, B.J., Gordon,C.T., Mannheim, G.B., & Rumsey, J.M. (1993). Dysfunctional attention in autistic savants. Journal of Clinical Experimental Neuropsychology, 15: 933 - 946.

Castelloe, P. & Dawson, G. (1993). Subclassification of children with autism and pervasive developmental disorder: A questionnaire based on Wing's subgrouping scheme. Journal of Autism and Developmental Disorders, 23: 229 - 241.

Chavis, D.A. & Pandya, D.N. (1976). Further observations on corticofrontal connections in the rhesus monkey. Brain Research, 117: 369 - 386.

Chess, S. (1971). Autism in children with congenital rubella. Journal of Autism and Childhood Schizophrenia, 1: 33 - 47.

Chiron, C., Leboyer, M., Leon, M., Jambaque, I., Nuttin, C., & Syrota, A. (1995). SPECT of the brain in childhood autism. Evidence for a lack of normal hemispheric asymmetry. Developmental Medicine and Child Neurology, 37: 849 - 860.

Chua, P, & Dolan, R.J. (2000). Neurobiology of anxiety and anxiety-related disorders: A functional neuroimaging perspective. In J.C. Mazziotta, A.W. Toga & R.S.J. Frackowiak (Eds) Brain Mapping: The Disorders, Academic Press, San Diego, 509 - 522.

Chugani, H.T. (1998). A critical period of brain development: Studies of cerebral glucose utilization with PET. Preventive Medicine, 27: 184 - 188.

Ciesielski, K.T., Courchesne, E., Akshoomoff, N.A., & Elmasion, R. (1990). Event related potentials in intermodality divided selective attention task in autism. Journal of Clinical Experimental Neuropsychology, 12: 77.

Ciesielski, K.T., Knight, J.E., Prince, R.J., Harris, R.J. & Handmaker, S.D. (1995) Event-related potentials in cross-modal divided attention in autism. Neuropsychologia, 33: 225 - 246.

Clarke, J.M., & Zaidel, E. (1994). Anatomical-behavioral relationships : corpus callosum morphometry and hemispheric specialization. Behavioral Brain Research, 64: 185 - 202.

Cohen, D., & Johnson, M. (1967). Cardiovascular correlates of attention in normal and psychiatrically disturbed children. Archives of General Psychiatry, 18: 565 - 567.

Corbetta, M., Miezin, F.M., Shulman, G.L., & Petersen, S.E. (1991). In: D.J. Chadwick and J. Whelan (Eds.), Exploring Brain Functional Anatomy with Positron Tomography. Wiley, Chichester. pp. 165 - 180.

Corbetta, M., Miezin, F.M.,Shulman, G.L., & Petersen, S.E. (1993) . A PET study of visuospatial attention. The Journal of Neuroscience, 13: 1202 - 1226.

Courchene, E. (1987). A neurophysiological view of autism. In Neurobiological Issues of Autism, E. Schopler, and G.B. Mesibove (Eds.). Plenum Press, New York.

Courchesne, E. (1991). Neuroanatomic imaging in autism. Pediatrics, S: 781 - 790.

Courchene, E. (1995). New evidence of cerebellar and brainstem hypoplasia in autistic infants, children and adolescents: The MR imaging study by Hashimoto and colleagues. Journal of Autism and Developmental Disorders, 25: 19 - 22.

Courchesne, E., Kilman, B., Galambos, R., & Lincoln, A. J. (1984). Autism: Processing of novel auditory information assessed by event-related brain potentials. Electroencephalography and Clinical Neurophysiology, 59 : 238 - 248.

Courchesne, E., Lincoln, A.J., Kilman, B., & Galambos, R. (1985). Event-related potential correlates of the processing of novel visual and auditory information in autism. Journal of Autism and Developmental Disorders, 15: 55 - 76.

Courchesne, E., Yeung-Courchesne, R., Press, G.A., Hesselink, J.R. & Jernigan, T.L. (1988). Hypoplasia of cerebellar vermal lobules VI and VII in autism. New England Journal of Medicine, 318: 1349 - 1354.

Courchesne, E., Townsend, J., Akshoomoff, N.A., Saitoh, O., Yeung-Courchesne, R., Lincolne, A.J., James, H.E., Haas, R.H., Schreibman, L. & Lau, L. (1994). Impairment in shifting attention in autistic and cerebellar patients. Behavioral Neuroscience, 108: 848 - 865.

Creutzfeldt, O., Ojemann, G. & Lettich, E. (1989). Neuronal activity in the human lateral temporal lobe. I. Responses to speech. Experimental Brain Research, 77: 451 - 475.

Critchley, H.D., Daly, E.M., Bullmore, E.T., Williams, S.C.R., Van Amelsvoort, T., Robertson, D.M., Rowe, A., Phillips, M., McAlonan, G., Howlin, P. & Murphy, D.G.M. (2000). The functional neuroanatomy of social behavior. Changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain, 123: 2203 - 2212.

Damasio, A.R., (1979). Frontal lobe dysfunction. In K. Heilman and E. Valenstein (Eds.), Clinical Neuropsychology. Oxford University Press, Oxford, England.

Damasio, A.R. (1985). Prosopagnosia. Trends in Neurosciences, 8: 132 - 135.

Damasio, A.R. & Maurer, R.G. (1978). A neurological model for childhood autism. Archives of Neurology, 35: 777 - 786.

Damasio, A.R., Grabowski, T.J., Tranel, D., Hitchwa, R.D. Damasio, A.R. (1996). A neural basis for lexical retrieval, Nature, 380: 499 - 505.

Damasio, A.R. & Van Hoesen, G.W. (1983). Emotional disturbances associated with focal lesions of the limbic frontal lobe. In: K.M. Heilman, and P. Satz (Eds.), The Neuropsychology of Human Emotion. Guilford, New York. pp. 85 - 110.

Darby, D.G. (1983). Sensory aprosodia: A clinical clue to lesions of the inferior division of the right middle cerebral artery? Neurology, 43: 567 - 572.

Darby, J.K. (1976). Neuropathologic aspects of psychosis in children. Journal of Autism Childhood Schizophrenia, 6: 339 - 352.

Davatzikos, C. & Resnick, S.M. (1998). Sex differences in anatomic measures of interhemispheric connectivity: Correlations with cognition in women but not men. Cerebral Cortex, 8: 635 - 640.

Davies, S., Bishop, D., Manstead, A.S.R., & Tantam, D. (1994). Face perception in children with autism and asperger's syndrome. Journal of Child Psychology and Psychiatry, 35: 1033 - 1057.

Dawson, G. (1996). Brief Report: Neuropsychology of autism: A report on the state of the science. Journal of Autism and Developmental Disorders, 26: 179 - 184.

Dawson, G. & Fernald, M. (1987). Perspective-taking ability and its relationship to the social behavior of autistic children. Journal of Autism and Developmental Disorders, 17: 487 - 498.

Dawson, G. & Lewy, A. (1989). Reciprocal subcortical - cortical influences in autism. In G. Dawson (Ed.) Autism: Nature, Diagnosis and Treatment. New York, Guilford. pp. 145 - 173.

Dawson, G., Hill, D, Spencer, A. & Galpert,L. (1990). Affective exchanges between young autistic children and their mothers. Journal of Abnormal Child Psychology, 18: 335 - 345.

Dawson, G. Klinger, L.G., Panagiotiedes, H., Lewy, A. & Castelloe, P. (1995). Subgroups of autistic children based on social behavior display distinct patterns of brain activity. Journal of Abnormal Child Psychology, 23: 569 - 583.

Dawson, G., Meltzoff, A.N., Osterling, J., Rinaldi, J. & Brown, E. (1998). Children with autism fail to orient to naturally occurring social stimuli. Journal of Autism and Developmental Disorders, 28: 479 - 485.

Denckla, M.B. (1986). New diagnostic criteria for autism and related behavioral disorders - Guidelines for research protocols. Journal of the American Academy of Child Psychiatry, 25: 221 - 224.

Deonna, T., Ziegler, A.L., Moura-Serra, J. & Innocenti, G. (1993). Autistic regression in relation to limbic pathology and epilepsy: report of two cases. Developmental Medicine and Child Neurology, 35: 166 - 176.

Delong, G.R. (1978). A neuropsychological interpretation of infantile autism. In M. Rutter & E. Schopler (Eds.), Autism: A reappraisal of concepts and treatment. New York: Plenum. pp. 207 - 218.

Deutsch, R.D., Kling, A. & Steklis, H.D., (1979). Influence of frontal lobe lesions on behavioral interactions in man. Research Communications in Psychology, Psychiatry and Behavior, 4: 415 - 431.

Devinsky, O., Morrell, M.J. & Vogel, B.A. (1995). Contributions of anterior cingulate cortex to behavior. Brain, 118: 279 - 306.

DeVolder, A., Bol, A., Michel, C., Congneau, M. & Goffinet, A. (1987). Brain glucose metabolism in children with the autistic syndrome: Positron tomography analysis. Brain Development, 9: 581 - 587.

Dimberg, U. (1990). Facial electromyography and emotion reactions. Psychophysiology, 27: 481 - 494.

Dubois, S., Rossion, B., Schiltz, C., Bodart, J.M., Michel, C., Bruyer, R. & Crommelinck, M. (1999). Effect of familiarity on the processing of human faces. Neuroimage, 9: 278 - 289.

Egaas, B., Courchesne, E. & Saito,O. (1995). Reduced size of corpus callosum in autism. Archives of Neurology, 52: 794 - 801.

Ekman, P. & Friesen, W. (1975). Pictures of Facial Affect. Consulting Psychologists Press, Palo Alto, California.

Elliott, R. & Dolan, R.J. (1998). The neural response in short-term visual recognition memory for perceptual conjunctions. Neuroimage, 7: 14 - 22.

Elliot, R., Dolan, R.J. & Frith, C.D. (2000). Dissociable functions in the medial and lateral orbitofrontal cortex: Evidence from Human Neuroimaging Studies. Cerebral Cortex, 10: 308 - 317.

Ellis, H.D. (1992). The development of face processing skills. Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences, 335: 105 - 111.

Fahy, F.L., Riches, I.P. & Brown, M.W. (1993). Neuronal activity related to visual recognition memory: Long term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. Experimental Brain Research, 96; 457 - 472.

Farah, M.J. (1990). Visual agnosia. Cambridge, MA; MIT Press.

Fein, D., Lucci, D., Braverman, M. & Waterhouse, L. (1992). Comprehension of affect in context in children with pervasive developmental disorders. Journal of Child Psychology and Psychiatry, 33: 1157 - 1167.

Felleman, D.J. & Van Essen, D.C. (1991). Distributed hierarchical processing in the primate cerebral cortex. Cerebral Cortex, 1: 1 - 47.

Filipek, P.A. (1995). Quantitative magnetic resonance imaging in autism: the cerebellar vermis. Current Opinions in Neurology, 8: 134 - 138.

Filipek, P.A. (1996). Brief Report: Neuroimaging in autism: The state of the science 1995. Journal of Autism and Developmental Disorders, 26: 211 - 215.

Filipek, P.A., Richelme, C., Kennedy, D.N., Radenmacher, J., Pitcher, D.A., Zidel, S. & Caviness, V.S. (1992). Morphometric analysis of the brain in developmental language disorders and autism (Abstract). Annals of Neurology, 32: 475.

Fink, G.R., Dolan, R.J., Halligan, P.W., Marshall, J.C. & Frith, C.D. (1997). Space-based and object-based visual attention: shared and specific neural domains. Brain, 120: 2013 - 2028.

Fombonne, E., Roge, B., Claverie, J., Courty, S. & Fremolle, J. (1999). Microcephaly and macrocephaly in autism. Journal of Autism and Developmental Disorders, 29: 113 - 119.

Frakowiak, R.S. & Tempini, M.L. (1998). The neural systems sustaining face and proper-name processing. Brain, 121: 2103 - 2118.

Franzen, E.A. & Myers, R.E. (1973). Neural control of social behavior: prefrontal and anterior temporal control. Neuropsychologia, 11: 141 - 157.

Freeman, B.J., Rivto, E.R., Needleman, R. & Yokota, A. (1985). The stability of cognitive and linguistic parameters in autism: A five-year prospective study. Journal of the American Academy of Child Psychiatry, 24: 459 - 464.

Fried, I., Mateer, C., Ojemann, G., Wohns, R. & Fedio, P. (1982). Organization of visuospatial functions in human cortex. Brain, 105: 349 - 371.

Friedman, E. (1969). The autistic syndrome and phenylketonuria. Schizophrenia, 1: 249 - 261.

Friston, K.J. (1997). Images of the future: A philosophical coda. In: R.S.J. Frackowiak, K.J. Friston, C.D. Frith, R.J. Dolan & J.C. Mazziotta (Eds). Human Brain Function, Academic Press, San Diego. pp. 329 - 366.

Friston, K.J. (1998). Imaging neuroscience: Principles or maps? Proceedings of the National Academy of Science, 95: 796 - 802.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.B., Heather, J.D. & Frackowiak, R.S.J. (1995a). Spatial registration and normalization of images. Human Brain Mapping -available via FTP and located in SPM 95_Papers.

Friston, K.J., Holmes, A.B., Worsley, K.J., Poline, J.B., Frith, C.D. & Frackowiak, R.S.J. (1995-b). Statistical parametric maps in functional imaging: A general approach. Human Brain Mapping - available via FTP and located in SPM 95_Papers.

Frith, U. (1989). Autism: Explaining the Enigma. Oxford: Basil Blackwell.

Frith, C. (1991). Positron emission tomography studies of frontal lobe function: relevance to psychiatric disease. In: D.J. Chadwick and J. Whelan (Eds.), Exploring Brain Functional Anatomy with Positron Tomography. Wiley, Chichester. pp. 181 -197.

Frith, C.D. & Dolan, R.J. (1997). Higher Cognitive Processes. In: R.S.J. Frackowiak, K.J. Friston, C.D. Frith, R.J. Dolan & J.C. Mazziotta (Eds). Human Brain Function, Academic Press, San Diego. pp. 329 - 366.

Frith, U. & Happe, F. (1994). Language and communication in autistic disorders. Philosophical Transcripts of the Royal Society of London, B, 346: 97 - 104.

Fuster, J.M. (1999). Synopsis of function and dysfunction of the frontal lobe. Acta Psychiatrica Scandinavia, 99: 51 - 57.

Gaffney, G.R., Kuperman, S., Tsai, L.Y. & Minchin, S. (1988). Morphological evidence for brainstem involvement in infantile autism. Biological Psychiatry, 24: 578 - 586.

Gaffney, G.R., Kuperman, S., Tsai, L.Y. & Minchin, S. (1989). Forebrain structure in infantile autism. Journal of the American Academy of Child and Adolescent Psychiatry, 28: 534 - 537.

Gainotti, G. (1972). Emotional behavior and hemispheric side of the lesion. Cortex, 8: 41 - 55.

Garber, H.J. & Ritvo, E.R. (1992). Magnetic resonance imaging of the posterior fossa in autistic adults. American Journal of Psychiatry, 49: 245 - 247.

Gauthier, I., Anderson A.W., Tarr, M.J, Skudlarski, P. & Gore, J.C. (1997). Levels of categorization in visual recognition studied using functional magnetic resonance imaging. Current Biology. 7: 645 -51.

Gazzaniga, M.S. (2000). Cerebral specialization and interhemispheric communication: Does the corpus callosum enable the human condition? Brain, 123: 1293 - 1326.

Gazzaniga, M.S. & Ledoux, J.E. (1978). The Integrated Mind. New York, Plenum Press.

Gazzaniga, M.S. & Smylie, C.S. (1990). Hemispheric mechanisms controlling voluntary and spontaneous facial expressions. Journal of Cognitive Neuroscience, 2: 239 - 245.

George, M.S., Costa, D.C., Kouris, K., Ring, H.A. & Ell, P.J. (1992). Cerebral blood flow abnormalities in adults with infantile autism. Journal of Nervous Mental Disease, 180: 413 - 417.

George, M.S., Ketter, T.A., Gill, D.S., Haxby, J.V., Ungerleider, L.G., Herscovitch, P. & Post, R.M. (1993). Brain regions involved in recognizing facial emotion or identity: An oxygen-15 PET study. Journal of Neuropsychiatry and Clinical Neurosciences, 5: 384 - 394.

George M.S., Ketter, T.A., Parekh, P.I., Horwitz, B., Herscovitch, P. & Post, R.M. (1995). Brain activity during transient sadness and happiness in healthy women. American Journal of Psychiatry, 152: 341 - 351.

George, M.S., Ketter, T.A., Parekh, P.I., Herscovitch, P. & Post, R.M. (1996a). Gender differences in regional cerebral blood flow during self-induced sadness or happiness. Biological Psychiatry, 40: 859 - 871.

George, M.S., Parekh, P.I., Rosinski, N., Ketter, T.A., Kimbrell, T.A., Heilman, K.M., Herscovitch, P. & Post, R.M. (1996b). Understanding emotional prosody activates right hemisphere regions. Archives of Neurology, 53: 665 - 670.

Gillbert, D. (1969). The young child's awareness of affect. Child Development, 39: 619 - 636.

Gillberg, C. & Coleman, M. (1996). Autism and medical disorders: A review of the literature. Developmental Medicine and Child Neurology, 38: 191 - 202.

Goldberg, J., Szatmari, P. & Nahmias, C. (1999). Imaging of autism: lessons from the past to guide studies in the future. Canadian Journal of Psychiatry, 44: 793 - 801.

Goldman-Rakic, P.S. (1988). Topography of cognition: Parallel distributed networks in primate association cortex {Review}. Annual Review of Neuroscience, 11: 137 - 156.

Gorno-Tempini, M.L., Price, C.J., Josephs, O., Vandenberghe, R., Cappa, S.F., Kapur, N., Frackowiak, R.S. & Tempini, M.L. (1998). The neural systems sustaining face and proper-name processing. Brain, 121: 2103 - 2118.

Grodd, W., Schneider, F., Klose, U. & Nagele, T. (1995). Functional magnetic resonance tomography of psychological functions exemplified by experimentally induced emotions. Radiologe, 35: 283 - 289.

Gross, A.L. & Ballif, B. (1991). Children's understanding of emotion from facial expressions and situations: A review. Developmental Review, 11: 368 - 398.

Gur, R.C., Skolnick, B.E. & Gur, R.E. (1994). Effects of emotional discrimination tasks on cerebral blood flow: Regional activation and its relation to performance. Brain and Cognition, 25: 271 - 286.

Gyulai, F.E., Firestone, L.L., Mintun, M.A., & Winter, P.M. (1996). In vivo imaging of human limbic responses to nitrous oxide inhalation. Anesthesia and Analgesia, 83: 291 - 298.

Hammes, J.G.W. & Langdell, T. (1981). Precursors of symbol formation and childhood autism. Journal of Autism and Developmental Disorders, 11: 331 - 346.

Happe, F.G.E. (1991) The autobiographical writings of three Asperger's Syndrome adults: Problems of interpretation and implications for theory. In. U. Frith (Ed.): Autism and Asperger Syndrome: Cambridge University Press, Cambridge. pp. 207 - 242.

Happe, F.G.E. (1994). Annotation: Current psychological theories of autism: The 'Theory of Mind' account and rival theories. Journal of Child Psychology and Psychiatry, 35: 215 - 229.

Happe, F., Ehlers, S., Fletcher, P., Frith, U., Johansson, M., Gillberg, C., Dolan, R., Frackowiak, R. & Frith, C. (1996). 'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. Neuroreport, 8: 197 - 201.

Hashimoto, T., Tayama, M., Miyazaki, M., Murakawa, K. & Kuroda, Y. (1994). MRI measurements of the brain stem and cerebellum in high functioning autistic children (Abstract). No To Hattatsu, 26: 3 - 8.

Hashimoto, T., Tayama, M., Murakawa, K., Yoshimoto, T., Miyazaki, M., Harada, M. & Kuroda, Y. (1995). Development of the brainstem and cerebellum in autistic patients. Journal of Autism and Developmental Disorders, 25: 1 - 17.

Hasselmo, M.E., Rolls, E.T. & Baylis, G.C. (1989). The role of expression and identity in the face-selective responses of neurons in the temporal visual cortex of the monkey. Behavioural Brain Research, 32: 203 - 218.

Hauck, M., Fein, D., Waterhouse, L. & Feinstein, C. (1995). Social initiations by autistic children to adults and other children. Journal of Autism and Developmental Disorders, 25: 579 - 595.

Haxby, J.V., Horwitz, B., Ungerleider, L.G., Maisog, J.M., Pietrini, P. & Grady, C.L. (1994). The functional organization of human extrastriate cortex: A PET-rCBF study of selective attention to faces and locations. The Journal of Neuroscience, 14: 6336 - 6353.

Haxby, J. V., Ungerleider, L. G., Horwitz, B., Maisog, J.M., Rapoport, S.I. & Grady, C.L. (1996). Face encoding and recognition in the human brain. Proceedings of the National Academy of Science U.S.A., 93: 922 - 927.

Haxby, J.V., Martin, A., Clark, V.P., Hoffman, E.A. Schouten, J.L., Ungerleider, L.G. (1997). The processing of faces, inverted faces and other objects in the ventral object vision pathway. Neuroimage, 5: S4.

Haznedar, M.M., Buchsbaum, M.S., Metzger, M., Solimando, A., Spiegel-Cohen, J., & Hollander, E. (1997). Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. American Journal of Psychiatry, 154: 1047 - 1050.

Heilman, K.M. (1997). The neurobiology of emotional experience. Journal of Neuropsychiatry and Clinical Neurosciences, 9: 439 - 448.

Heilman, K.M., Bowers, D., Speedie, L. & Coslett, B. (1984). Comprehension fo affective and nonaffective prosody. Neurology, 34: 917 - 921.

Heilman, K.M., Watson, R.T & Valenstein, E. (1994). Localization of lesions in neglect and related disorders. In: A.Kertesz (Ed). Localization and neuroimaging in neuropsychology. Academic Press, San Diego. pp. 495 - 524.

Heller, W. (1993). Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. Neuropsychology, 7: 476 - 489.

Herold, S., Frackowiak, R., LeCouteur, A., Rutter, M., & Howlin, P. (1988). Cerebral blood flow and metabolism of oxygen and glucose in young autistic adults. Psychological Medicine, 18: 823 - 831.

Herscovitch, P., Markham, J. & Raichle, M.E. (1983). Brain blood flow measured with intravenous H2(15)O. I. Theory and error analysis. Journal of Nuclear Medicine, 24: 782 - 789.

Herscovitch, P., Raichle, M.E., Kilbourn, M.R. & Welch, M.J. (1987). Positron emission tomographic measurement of cerebral blood flow and permeability-surface area product of water using [15O]water and [11C]butanol. Journal of Cerebral Blood Flow Metabolism, 7: 527 - 542.

Heywood, C.A. & Cowey, A. (1992). The role of the 'face-cell' area in the discrimination and recognition of faces by monkeys. Philosophical Transcripts of the Royal Society of London, B Biological Science, 335: 31 - 38.

Heywood C.A. & Cowey, A. (1993). Colour and face perception in man and monkey: the missing link. In B. Gulyas, D. Ottoson, D & P.E. Roland (Eds.), Functional Organisation of Human Visual Cortex. Oxford, Pergamon Press. pp. 195 - 210.

Hobson, R.P. (1991). Methodological issues for experiments on autistic individuals' perception and understanding of emotion. Journal of Child Psychology and Psychiatry, 32: 1135 - 1158.

Hobson, R.P. & Lee, A. (1989). Emotion-related and abstract concepts in autistic people: evidence from the British Picture Vocabulary Scale. Journal of Autism and Developmental Disorders, 19: 601 - 623.

Hobson, R.P., Ouston, J. & Lee, A. (1988a). What's in a face? the case of autism. British Journal of Psychology, 79: 441 - 453.

Hobson, R.P., Ouston, J. & Lee, A. (1988b). Emotion recognition in autism: coordinating faces and voices. Psychological Medicine, 18: 911 - 923.

Hobson, R.P., Ouston, J. & Lee, A. (1989). Naming emotion in faces and voices: Abilities and disabilities in autism and mental retardation. British Journal of Developmental Psychology, 16: 454 - 464.

Hof, P.R., Knabe, R., Bovier, P., Bouras, C. (1991). Neuropathological observations in a case of autism presenting with self-injury behavior. Acta Neuropathologica (Berlin), 82: 321 - 326.

Holttum, J.R., Minshew, N.J., Sanders, R.S. & Phillips, N.E. (1992). Magnetic resonance imaging of the posterior fossa in autism. Biological Psychiatry, 32: 1091 - 1101.

Honda, H., Shimizu, Y, Misumi, K., Niimi, M. & Ohashi, Y. (1996). Cumulative incidence and prevalence of childhood autism in children in Japan. British Journal of Psychiatry, 169: 228 - 235.

Hoon, A.H. Jr, & Reiss, A.L. (1992). The mesial-temporal lobe and autism: case report and review. Developmental Medicine Child Neurology, 34: 252 - 259.

Hornak, J., Rolls, E.T. & Wade, D. (1996). Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia, 34: 247 - 261.

Horwitz, B. & Rumsey, J.M. (1994). Positron emission tomography: Implications for cerebral dysfunction in autism. In: The Neurobiology of Autism, Bauman, M.L. & Kemper, T.L. Johns Hopkins University Press, London.

Horwitz, B., Rumsey, J.M., Grady, C.L. & Rapoport, S.I. (1988). The cerebral metabolism landscape in autism: Intercorrelations of regional glucose utilization. Archives of Neurology, 45: 749 - 755.

Hsu, M., Yeung-Courchesne, R., Courchesne, E. & Press, G.A. (1991). Absence of magnetic resonance imaging evidence of pontine abnormality in infantile autism. Archives of Neurology, 48: 1160 - 1163.

Hunt, A. & Shepard, C. (1993). A prevalence study of autism in tuberous sclerosis. Journal of Autism and Developmental Disorders, 23: 323 - 339.

Inglis J., Ruckman, M., Lawson, J.S., MacLean, A.W., & Monga, T.N. (1982). Sex differences in the cognitive effects of unilateral brain damage. Cortex,18: 257 - 275

Jacobson, J.W. & Ackerman, L.J. (1990). Differences in adaptive functioning among people with autism or mental retardation. Journal of Autism and Developmental Disorders, 20: 205 - 220.

Jacobsen, L.K., Giedd, J.N., Berquin, P.C., Krain, A.L., Hamburger, S.D., Kumra, S. & Rapoport J.L (1997). Quantitative morphology of the cerebellum and fourth ventricle in childhood-onset schizophrenia. American Journal of Psychiatry, 154: 1663 - 1669.

Jolliffe, T. & Baron-Cohen, S. (1997). Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? Journal of Child Psychology and Psychiatry, 38: 527 - 534.

Kanner, L. (1943). Autistic disturbances of affective contact. Nervous Child, 2: 217 - 250.

Kanner, L. (1973). The birth of early infantile autism. Journal of Autism and Childhood Schizophrenia, 3: 93 - 95

Kanwisher N., Chun, M.M. & McDermott, J. (1996). fMRI in individual subjects reveals loci in extrastriate cortex differentially sensitive to faces and objects. Investigative Opthamology and Visual Science, 37: S193.

Kanwisher, N., McDermott, J. & Chun, M.M. (1997). The fusiform area: A module in human extrastriate cortex specialized for face perception. The Journal of Neuroscience, 17: 4302 - 4311.

Kapur, S., Tulving, E., Cabeza, R., McIntosh, A.R., Houle, S. & Craik, F.I. (1996). The neural correlates of intentional learning of verbal materials: A PET study in humans. Brain Research, Cognitive Brain Research, 4: 243 -249.

Kapur, S., Jones, C., DaSilva, J., Wilson, A. & Houle, S. (1997). Reliability of a simple non-invasive method for the evaluation of 5-HT2 receptors using [18F]-setoperone PET imaging. Nuclear Medicine Communications, 18: 395 - 399.

Karatekin, C., Lazareff, J.A. & Asarnow, R.F. (1999). Parallel and serial search in two teenagers with lesions of the mesial parietal cortex. Neuropsychologia, 37: 1461 - 1468.

Karmiloff-Smith, A., Klima, E., Bellugi, U., Grant, J. & Baron-Cohen, S. (1995). Is there a social module? Language, face processing and theory of mind in individuals with Williams Syndrome. Journal of Cognitive Neuroscience, 7: 196 - 208.

Kasari, C. Yirimiya, N., Mundy, P. & Sigman, M. (1986) Affect expressions: A comparison of autistic, MR and normal children. Paper presented at the annual meeting of the American Psychological Association, Washington, D.C.

Kasari, C., Sigman, M., & Mundy, P. & Yirimiya, N. (1990) Affective sharing in the context of joint attention interactions of normal, autistic and mentally retarded children. Journal of Autism and Developmental Disorders, 20: 87 - 100.

Kasari, C., Sigman, M.D., & Yirmiya, N. (1993). Focussed and social attention of autistic children in interactions with familiar and unfamiliar adults: A comparison of autistic, mentally retarded and normal children. Development and Psychopathology, 5: 403 - 414.

Kasari, C., Sigman, M., Baumgartner, P., & Stipek, D.J. (1993). Pride and mastery in children with autism. Journal of Child Psychology and Psychiatry, 34: 353 - 362.

Kawashima, R., Itoh, M., Hatazawa, J., Miyazawa, H., Yamada, K., Matsuzawa, T. & Fukuda, H. (1993). Changes of regional cerebral blood flow during listening to an unfamiliar spoken language. Neuroscience Letters, 161: 69 - 72.

Kimura, D. & Harshman, R.A. (1984). Sex differences in brain organization for verbal and non-verbal functions. Progress in Brain Research, 61: 423 - 439.

Kleiman, M.D., Neff, S., Rosman, N.P. (1992). The brain in infantile autism: are posterior fossa structures abnormal? Neurology, 42: 753 - 760.

Klingberg, T. & Roland, P.E. (1998). Right prefrontal activation during encoding, but not during retrieval, in a non-verbal paired-associates task. Cerebral Cortex, 8: 73 - 79.

Klinnert, M.D., Campos, J.J., Sorce, J.F., Emde, R.N. & Svejda, M. (1983). In R. Plutchik & H. Kellerman (Eds). Emotion: Theory, Research and Experience, Volume 2, Emotions in Early Development. Academic Press, New York. pp. 57 - 86.

Kolb, B. & Taylor, L. (1981). Effective behaviour in patients with localised cortical excisions: Role of lesion site and side. Science, 214: 89 - 91.

Kolb, B. & Wishaw, I.Q. (1990). Fundamentals of Human Neuropsychology. - 3rd ed. W.H. Freeman and Company, New York.

Kring, A.M. & Gordon, A.H. (1998). Sex difference in emotion: Expression, experience and physiology. Journal of Personality and Social Psychology, 74: 686 - 703.

LaBarbera, J.D., Izard, C.E., Vietze, P. & Parisi, S.A. (1976). Four- and six-month-old infants' visual responses to joy, anger, and neutral expressions. Child Development, 47: 535 - 538.

Lane, R.D., Reiman, E.M., Ahern, G.L., Schwartz, G.E. & Davidson, R.J. (1997). Neuroanatomical correlates of happiness, sadness, and disgust. American Journal of Psychiatry, 154: 926 - 933.

Lane, R.D., Reiman, E.M., Axelrod, B., Yun, L.-S., Holmes, A. & Schwartz, G.E. (1998). Neural correlates of levels of emotional awareness: Evidence of an interaction between emotion and attention in the anterior cingulate cortex. Journal of Cognitive Neuroscience, 10: 525 - 535.

Langdell, T. (1978). Recognition of faces: An approach to the study of autism. Journal of Child Psychology and Psychiatry, 19: 255 - 268.

Lammertsma, A.A. & Mazoyer, B.M. (1990). EEC concerted action on cellular degeneration and regeneration studied with PET: Modelling expert meeting blood flow measurement with PET. European Journal of Nuclear Medicine, 16: 808 - 812.

LeDoux, J. (1987). Cognitive-emotional interactions in the brain. Cognition and Emotion, 3: 267 - 289.

Leslie, A.M. (1987). Pretence and representation: the origins of "theory of mind". Psychological Review, 94: 412 - 426.

Leventhal, H. & Tomarken, A.J. (1986). Emotion: Today's problems. Annual Review of Psychology, 37: 565 - 610.

Lord, C. (1984). Development of peer relations in children with autism. In F. Morrison, C., Lord & D. Keating (Eds.). Applied Developmental Psychology. Academic Press, New York. pp. 165 - 230.

Lotze, M., Montoya, P., Erb, M., Hulsmann, E., Flor, H., Klose, U., Birbaumer, N. & Grodd, W. Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study. Journal of Cognitive Neuroscience, 11: 491 - 501.

Lotze, M., Erb, M., Flor, H., Huelsmann, E., Godde, B., Grodd, W. (2000). fMRI evaluation of somatotopic representation in human primary motor cortex. Neuroimage, 11: 473 - 481.

Loveland, K.A. & Landry, S.H. (1986). Joint attention and language in autism and developmental language delay. Journal of Autism and Developmental Disorders: 16, 335- 349.

Macaluso, E., Frith, C. & Driver, J. (2000). Modulation of human visual cortex by crossmodal spatial attention. Science, 289: 1206 - 1208.

MacDonald, H., Rutter, M., Howlin, P., Rios, P., LeCouteur, A., Evered, C. & Folstein, S. (1989). Recognition and expression of emotional cues by autistic and adults. Journal of Child Psychology and Psychiatry, 30: 865 - 877.

Mandal, M.K., Asthana, H.S., Maitra, S.(1998). Right hemisphere damage impairs the ability to process emotional expressions of unusual faces. Behavior Modification 22: 167 - 176.

McCormick, C.M. & Witelson, S.F. (1994). Functional cerebral asymmetry and sexual orientation in men and women. Behavioral Neuroscience, 108: 525 - 531.

McGlone, J. (1977). Sex differences in the cerebral organization of verbal functions in patients with unilateral brain lesions. Brain, 100: 775 - 793.

McGlone, J. (1978). Sex differences in functional brain asymmetry. Cortex, 14: 122 - 128.

McGlone, J. (1980). Sex differences in human brain asymmetry: a critical survey. Behavior Brain Science, 3: 215 - 263.

McGlone, J. (1981). Sexual variation in behaviour during spatial and verbal tasks. Canadian Journal of Psychology, 35: 277 - 282.

Meltzoff, A.N. (1990). Towards a developmental cognitive science. The implications of cross-modal matching and imitation for the development of representation and memory in infancy. Annals of the New York Academy of Sciences, 608: 1 - 31.

Mesulam, M.-M. (1998). From sensation to cognition. Brain, 121: 1013 - 1052.

Mesulam, M.M. (1999). Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. Philosophical Transcripts of the Royal Society of London, Series B, Biological Sciences, 354: 1325 - 1346.

Meyer, J.H., Brown, G.M., Houle, S., DaSilva, J.N., Wilson, A.A. & Kapur, S. (1996). Neuromodulation of frontal and temporal cortex by intravenous d-fenfluramine: an [15O]H2O PET study in humans. Neuroscience Letters, 207: 25 - 28.

Milner, B. (1964). Some effects of frontal lobectomy in man. In J.M. Warren & K. Akert (Eds.), The Frontal Granular Cortex and Behavior. McGraw-Hill, New York.

Minshew, N.J. (1991). Indices of neural function in autism: Clinical and biologic implications. Pediatrics, 87(S): 774 - 780.

Minshew, N.J. (1996). Brief report: brain mechanisms in autism: functional and structural abnormalities. Journal of Autism and Developmental Disorders, 26: 205 - 209.

Mintun, M.A., Fox, P.T. & Raichle, M.E. (1989). A highly accurate method of localizing regions of neuronal activation in the human brain with positron emission tomography. Journal of Cerebral Blood Flow and Metabolism, 9: 96 - 103.

Mishkin, M., Ungerleider, L.G. & Macko, K.A. (1983). Object vision and spatial vision: Two cortical pathways. Trends in Neurosciences, 6: 414 - 417.

Moore, C.J. & Price, C.J. (1999). A functional neuroimaging study of the variables the generate category-specific object processing differences. Brain, 122: 943 - 962.

Morris, J.S., Frith, C.D., Perrett, D.I., Rowland, D., Young, A.W., Calder, A.J. & Dolan, R.J. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. Nature, 383: 812 - 815.

Morrow L., Vrtunski P.B., Kim Y., Boller F. (1981). Arousal responses to emotional stimuli and laterality of lesion. Neuropsychologia, 19: 65 - 71.

Muller, R., Chugani, D.C., Behen, M.E., Rothermel., R.D., Muzik, O., Chakraborty, P.K., Chugani, H.T. (1998). Impairment of dento-thalamic pathway in autistic men: language activation data from positron emission tomography. Neuroscience Letters, 245: 1 - 4.

Mundy, P. (1995). Joint attention and social-emotional approach behavior in children with autism. Development and Psychopathology, 7: 63 - 82.

Nagao, S. (1992). Different roles of flocculus and ventral paraflocculus for oculomotor control in the primate. Neuroreport. 3: 13 - 16.

Nakamura, K., Kawashima, R., Ito, K., Sugiura, M., Kato, T., Nakamura, A., Hatano, K., Nagumo, S., Kubota, K., Fukuda, H. & Kojima, S. (1999). Activation of the right inferior frontal cortex during assessment of facial emotion. Journal of Neurophysiology, 82: 1610 - 1614.

Narumoto, J., Yamada, H., Iidaka, T., Sadato, N., Fukui, K., Itoh, H. & Yonekura, Y. (2000). Brain regions involved in verbal or non-verbal aspects of facial emotion recognition. NeuroReport, 11: 2571 - 2576.

Neil, B.C.J. (1985). Background Radiation Doses to the Public in Ontario. Ontario Hydro Report #SSD-85-1.

Nopoulos, P.C., Ceilley, J.W., Gailis, E.A. & Andreasen, N.C. (1999). An MRI study of cerebellar vermis morphology in patients with schizophrenia: evidence in support of the cognitive dysmetria concept. Biological Psychiatry, 46: 703 - 711.

Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 9: 97 - 113.

Ornitz, E.M. (1989). Autism at the interface between sensory and information processing. In: G. Dawson (Ed.) Autism: Nature, Diagnosis and Treatment. Guilford, New York. pp. 174 - 207.

Osterling, J. & Dawson, G. (1994). Early recognition of children with autism: A study of first birthday home videotapes. Journal of Autism and Developmental Disorders, 24: 249 - 257.

Ott, R.J., Flower, M.A., Babich, J.W. & Marsden, P.K. (1988). The physics of radioisotope imaging. In S. Webb, (Ed.). The Physics of Medical Imaging. Institute of Physics Publishing, Bristol. pp. 142 - 318.

Owen, A.M., Milner, B., Petrides, M., Evans, A.C. (1996). Memory for object features versus memory for object location: A positron-emission tomography study of encoding and retrieval processes. Proceedings of the National Academy of Science, USA, 93: 9212 - 9217.

Ozonoff, S., Pennington, B. & Rogers, S.J. (1990) Are there emotion perception deficits in young autistic children. Journal of Child Psychology and Psychiatry, 31: 343 - 361.

Ozonoff, S., Pennington, B. & Rogers, S.J. (1991) Executive function deficits in high functioning autistic individuals. Journal of Child Psychology & Psychiatry, 32: 1081 - 1105.

Ozonoff, S. & Miller, J.N. (1995). Teaching theory of mind: a new approach to social skills training for individuals with autism. Journal of Autism and Developmental Disorders, 25: 415 - 433.

Pakkenberg, B. & Gundersen, H.J.G. (1997). Neocortical neuron number in humans: Effect fo sex and age. The Journal of Comparative Neurology, 384: 312 - 320.

Parving, A. (1999). The need for universal neonatal hearing screening - some aspects of epidemiology and identification. Acta Paediatrica, S 88: 69 - 72.

Peper, M. & Irle, E. (1997). The decoding of emotional concepts in patients with focal cerebral lesions. Brain and Cognition, 34: 360 - 387.

Perrett, D.I., Oram, M.W., Harries, M.H, Bevan, R., Hietanen, J.K., Benson, P.J. & Thomas, S. (1991). Viewer-centered and object-centered coding of heads in the macaque temporal cortex. Experimental Brain Research, 88: 159 - 173.

Petrides, M., Alivisatos, B., Evans, A.C. & Meyer, E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proceedings of the National Accademy of Science, 90: 873 - 877.

Phelps, M.E. & Mazziotta, J.C. (1985). Positron emission tomography: Human brain function and biochemistry. Science, 228: 799 - 809.

Philips, W., Baron-Cohen, S. & Rutter, M. (1992). The role of eye contact in the detection of goals: evidence from normal toddlers and children with autism or mental handicap. Developmental Psychopathology, 4: 375 - 383.

Phillips, M.L., Young, A.W., Senior, C., Brammer, M., Andrews, C., Calder, A.J., Bullmore, E.T., Perrett, D.I., Rowland, D., Williams, S.C.R., Gray, J.A. & David, A.S. (1997). A specific neural substrate for perceiving facial expressions of disgust. Nature, 389: 495 - 498.

Piven, J., Berthier, M.L., Starkstein, S.E., Nehme, E., Pearlson, G. & Folstein, S. (1990). Magnetic resonance imaging evidence for a defect of cerebral cortical development in autism. American Journal of Psychiatry, 147: 734 - 739.

Piven, J., Nehme, E., Simon, J., Barta, P., Pearlson, G. & Folstein, S.E. (1992). Magnetic resonance imaging in autism: Measurement of the cerebellum, pons, and fourth ventricle. Biological Psychiatry, 31: 491 - 504.

Piven, J. & Folstein, S. (1994). The genetics of autism. In: M.L. Bauman & T.L. Kemper, (Eds.). The Neurobiology of Autism. Johns Hopkins Unversity Press, London.

Piven, J., Arndt, S., Bailey, J., Havercamp, S., Andreasen, N.C. & Palmer, P. (1995). An MRI study of brain size in autism. American Journal of Psychiatry, 152: 1145 - 1149.

Piven, J., Bailey, J., Ranson, B.J. & Arndt, S. (1997). An MRI study of the corpus callosum in autism. American Journal of Psychiatry, 154: 1051 - 1056.

Piven, J., Bailey, J., Ranson, B.J. & Arndt, S. (1998). No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. Journal of Autism and Developmental Disorders, 28: 105 - 110.

Porro, C.A., Francescato, M.P., Cettolo, V., Diamond, M.E., Baraldi, P., Zuiani, C., Bazzocchi, M. & di Prampero, P.E. (1996). Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. Journal of Neuroscience, 16: 7688 - 7698.

Posner, M.I. (1994). Attention: The mechanisms of consciousness. Proceedings of the National Academy of Sciences of the USA, 91: 7398 - 7403.

Price, C.J., Moore, C.J., Humphreys, G.W., Frackowiak, R.S. & Friston, K.J. (1996). The neural regions sustaining object recognition and naming. Proceedings of the Royal Society of London. Series B: Biological Sciences 263: 1501 - 1507.

Price, C.J., Wise, R.J.S., Warburton, E.A., Moore, C.J., Howard, D., Patterson, K., Frackowiak, R.S.J. & Friston, K.J. (1996). Hearing and saying: The functional neuro-anatomy of auditory word processing. Brain, 119: 919 - 931.

Pring, L., Hermelin, B. & Heavey, L. (1995). Savants, segments, art and autism. Journal of Child Psychology and Psychiatry, 36: 1065 - 1076.

Prior, M. (1979). Cognitive abilities and disabilities in infantile autism: A review. Journal of Abnormal Child Psychology, 7: 357 - 380.

Prior, M.R., Tress, B., Hoffman, W.L. & Boldt, D. (1984). Computed tomographic study of children with classic autism. Archives of Neurology, 41: 482 - 484.

Puce, A., Allison, T., Gore, J.C. & McCarthy, G. (1995). Face-sensitive regions in human extrastriate cortex studied by functional MRI. Journal of Neurophysiology, 74: 1192 - 1199.

Puce, A., Allison, T., Asgari, M., Gore, J.C. & McCarthy, G. (1996). Differential sensitivity of human visual cortex to faces, letterstrings, and textures: A functional magnetic resonance imaging study. The Journal of Neuroscience, 16: 5205 - 5215.

Raichle, M.E, Martin, W.R., Herscovitch, P., Mintun, M.A. & Markham, J. (1983). Brain blood flow measured with intravenous H2(15)O. II. Implementation and validation. Journal of Nuclear Medicine, 24: 790 - 798.

Rapin, I. (1991). Autistic children: Diagnosis and clinical features. Pediatrics, (S), 87: 751 - 760.

Rapin, I. (1997). Autism. The New England Journal of Medicine, 337: 97 - 104.

Rapin, I. & Katzman, R. (1998). Neurobiology of Autism. Annals of Neurology, 43: 7 - 14.

Rapin, I. (1994). Introduction and Overview. In: M.L. Bauman, & T.L. Kemper, The Neurobiology of Autism. Johns Hopkins University Press, London.

Reiman, E.M. (1997). The application of positron emission tomography to the study of normal and pathological emotions. Journal of Clinical Psychiatry, 58 (S16): 4 - 12.

Reiman, E.M., Lane, R.D., Ahern, G.L., Schwartz, G.E., Davidson, R.J., Frison, K.J., Yun, L.-S. & Chen, K. (1997). Neuroanatomical correlates of externally and internally generated human emotion. American Journal of Psychiatry, 154: 918 - 925.

Ring, H.A., Baron-Cohen, S., Wheelwright, S., Williams, S.C.R., Brammer, M., Andrew, C. & Bullmore, E.T. (1999). Cerebral correlates of preserved cognitive skills in autism: A functional MRI study of Embedded Figures Task performance. Brain, 122: 1305 - 1315.

Rivto, E.R., Freeman, B.J., Scheibel, A.B., Duong, T., Robinson, H., Guthrie, D. & Rivto, A. (1986). Lower purkinje cell counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSAC autopsy research report. American Journal of Psychiatry, 143: 862 - 866.

Rodier, P.M., Ingram, J. L., Tisdale, B., Nelson, S.& Romano, J. (1996). Embryological origin for autism: Developmental anomalies of the cranial nerve motor nuclei. The Journal of Comparative Neurology, 370: 247 - 261.

Rodier, P.M. (2000). The early origins of autism. Scientific American, 282: 56 - 63.

Rogers S. & Pennington, B.F. (1991). A theoretical approach to the deficits in infantile autism. Development and Psychopathology, 3: 137 - 162.

Roland, P.E. & Friberg, L. (1985). Localization of cortical areas activated by thinking. Journal of Neurophysiology, 53: 1219 - 1243.

Rumsey , J.M., Duara, R., Grady, C., Rapoport, L.J., Margolin, R.A., Rapoport, S.T. & Cutler, N.R. (1985). Brain metabolism in autism. Resting cerebral glucose utilization rates as measured with positron emission tomography. Archives of General Psychiatry, 42: 448 - 455.

Rutter, M.L. & Lockyer, L., (1967). A five to fifteen year follow-up study of infantile psychosis. I. Description of a sample. British Journal of Psychiatry, 113: 1169 - 1182.

Rutter, M.L., Greenfeld, D. & Lockyer, L., (1967). A five to fifteen year follow-up study of infantile psychosis II. Social and Behavioural Outcome. British Journal of Psychiatry, 113: 1183 - 1199.

Ryu, Y.H., Lee, J.D., Yoon, P.H., Kim, D.I., Lee, H.B., Shin, Y.J. (1999). Perfusion impairments in infantile autism on technetium-99m ethyl cysteinate dimer brain single-photon emission tomography: comparison with findings on magnetic resonance imaging. European Journal of Nuclear Medicine, 26: 253 - 259.

Sams, M., Hietanen, J.K., Hari, R., Ilmoniemi, R.J. & Lounasmaa, O.V. (1997). Face specific responses from the human inferior occipito-temporal cortex. Neuroscience, 77: 49 - 55.

Scaife, M. & Bruner, J. (1975). The capacity for joint visual attention in the infant. Nature, 253: 265 - 266.

Schmahmann, J.D. & Sherman, J.C. (1998). The cerebellar cognitive affective syndrome. Brain, 121: 561 - 579.

Schopler, E. & Mesibov, G.B. (Eds.). (1983). Autism in Adolescents and Adults. Plenum, New York.

Schultz, R.T., Gauthier, I., Klin, A., Fulbright, R.K., Anderson, A.W., Volkmar, F., Skudlarski, P., Lacadie, C., Cohen, D. & Gore, J.C. (2000). Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and asperger syndrome. Archives of General Psychiatry, 57: 331 - 340.

Sergent, J., Ohta, S. & Macdonald, B. (1992). Functional neuroanatomy of face and object processing. Brain, 115: 15 - 36.

Servan-Schreiber, D. & Perlstein, W.M. (1997). Pharmacologic activation of limbic structures and neuroimaging studies of emotions. Journal of Clinical Psychiatry, 58 (S) 16:13 - 15.

Shallice, T., Fletcher, P., Frith, C.D., Grasby, P., Frackowiak, R.S.J. & Dolan, R.J. (1994). Brain regions associated with acquisition and retrieval of verbal episodic memory. Nature, 368: 633 - 635.

Shaywitz, B.A., Shaywitz, S.E., Pugh, K.R., Constable, R.T., Skudlarski, P., Fullbright, R.K., Bronen, R.A., Fletcher J.M., Shankweiler, D.P. Katz, L. & Gore, J.C. (1995). Sex differences in the functional organization of the brain for language. Nature, 373: 607 - 609.

Sherrod, L. (1981). Issues in cognitive-perceptual development: the special case of social stimuli. In M.E. Lamb & L.R. Sherrod (Eds.), Infant social cognition: Empirical and theoretical considerations. Lawrence Erlbaum, Hillsdale, New Jersey. pp.11 - 36.

Shipp, S., de Jong, B.M., Zihl, J., Frackowiak, R.S.J. & Zeki, S. (1994). The brain activity related to residual motion vision in a patient with bilateral lesions of V5. Brain, 117: 1023 - 1038.

Sidorova, O.A. & Kostyunina, M.B. (1993). The participation of cortical areas of the brain in processes of the perception and reproduction of emotional states of man. Neuroscience and Behavioral Physiology, 23: 135 - 141.

Sigman, M., Kasari, C., Kwon, J.H. & Yirmiya, N. (1992). Responses to the negative emotions of others by autistic, mentally retarded and normal children. Child Development, 63: 796 - 807.

Siegel, B.V., Asarnow, R., Tanguay, P., Call, J.D., Abel, L., Ho, A., Lott, I. & Buchsbaum, M.S. (1992). Regional cerebral glucose metabolism and attention in adults with a history of childhood autism. Journal of Neuropsychiatry and Clinical Neuroscience, 4: 406 - 414.

Sigman, M., Arbelle, S. & Dissanayake, C. (1995). Current research findings on childhood autism. Canadian Journal of Psychiatry, 40: 289 - 294.

Smith, E. E., Jonides, J., Marshuetz, C. & Koeppe, R.A. (1998). Components of verbal working memory: Evidence from neuroimaging. Proceedings of the National Academy of Science, 95: 876 - 882.

Smith, I.M. and Bryson, S.E. (1994). Imitation and action in autism: A critical review. Psychological Bulletin, 116: 259 - 273.

Snow, M.E., Hertzig, M.E. & Shapiro, T. (1987). Expression of emotion in young autistic children. Journal of the American Academy of Child and Adolescent Psychiatry, 26: 836 - 838.

Starkstein, S.E., Federoff, J.P., Price, T.R., Leiguarda, R.C. & Robinson, R.G. (1994). Neuropsychological and neuroradiologic correlates of emotional prosody comprehension. Neurology, 44: 515 - 522.

Streit, M., Ioannides, A.A., Liu, L., Wolwer, W., Dammers, J., Gross, J., Gaebel, W. & Muller-Gartner, H.-W. (1999). Neurophysiological correlates of the recognition of facial expressions of emotion as revealed by magnetoencephalography. Cognitive Brain Research, 7: 481 - 491.

Stromland, K. & Miller, M.T. (1993). Thalidomide embryopathy: revisited 27 years later. Acta Ophthalmologica, 71: 238 - 245.

Szatmari, P. (1996). The search for autism genes: Current findings and future prospects. Paper Presented at the Geneva Centre Symposium, Toronto, Ontario, Canada, November 1996.

Talairach, J. & Tournoux, P. (1988). Co-Planar Sterotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging. Thieme, New York.

Trad, P.V., Bernstein, D., Shapiro, T. & Hertzig, M. (1993). Assessing the relationship between affective responsivity and social interaction in children with pervasive developmental disorder. Journal of Autism and Developmental Disorders, 23: 361 - 377.

Tranel, D., Damasio, A.R., & Damasio, H. (1988). Intact recognition of facial expression, gender and age in patients with impaired recognition of face identity. Neurology, 38: 690 - 696.

Tranel, D., Damasio, H.& Damasio, A.R. (1995). Double dissociation between overt and covert face recognition. Journal of Cognitive Neuroscience, 7: 425 - 432.

Tranel, D., Damasio, H.& Damasio, A.R. (1997). A neural basis of the retrieval of conceptual knowledge. Neuropsychologia, 35: 1319 - 1327.

Tucker, D.M. (1981). Lateral brain function, emotion and conceptualization. Psychological Bulletin, 89: 19 - 46.

Ungerleider, L.G. & Mishkin, M. (1982). In: D. J. Ingle, M. A. Goodale and R. J. W. Mansfield (Eds). Analysis of Visual Behavior. The MIT Press, London. pp. 549 - 586.

Ungerleider, L.G., Courtney, S.M. & Haxby, J.V. (1998). A neural system for human visual working memory. Proceedings of the National Academy of Science, 95: 883 - 890.

Van Essen, D.C., Drury, H.A., Joshi, S. & Miller, M.I. (1998). Functional and structural mapping of human cerebral cortex: solutions are in the surfaces. Proceedings of the National Academy of Science, 95: 788 - 795.

Van Lancker, D., Cornelius, C. & Kreiman, J. (1989). Recognition of emotional-prosodic meanings in speech by autistic, schizophrenic and normal children. Developmental Neuropsychology, 5: 207 - 226.

Volkow, N.D., Mullani, N., Gould, L.K., Adler, S.S. & Gatley, S.J. (1991). Sensitivity of measurements of regional brain activation with oxygen-15-water and PET to time of stimulation and period of image reconstruction. Journal of Nuclear Medicine, 32: 58 - 61.

Wagner, H.L., Buck, R. & Winterbotham, M. (1993). Communication of specific emotions: Gender differences in sending accuracy and communication measures. Journal of Nonverbal Behavior, 17: 29 - 52.

Wainwright, J.A. & Bryson, S.E. (1996). Visual-spatial orienting in autism. Journal of Autism and Developmental Disorders, 26: 423 - 438.

Waterhouse, L., Fein, D. & Modahl, C. (1996). Neurofunctional mechanisms in autism. Psychological Review, 103: 457 - 489.

Webster, M.J., Bachevalier, J., & Ungerleider, L.G. (1994). Connections of inferior temporal a areas TEO and TE with parietal and frontal cortex in macaque monkeys. Cerebral Cortex, 4: 470 - 483.

Weeks, S.J. & Hobson, R.P. (1987). The salience of facial expression for autistic children. Journal of Child Psychology and Psychiatry, 28: 137 - 152.

Wing, L. (1976). Diagnosis, clinical description and prognosis. In L. Wing (Ed.). Early Childhood Autism. Pergamon: Oxford, 15 - 48.

Wing, L. (1981). Asperger's syndrome: A clinical account. Psychological Medicine, 11: 115 - 129.

Wing, L. (1991). The relationship between Asperger's syndrome and Kanner's autism. In: Uta Frith (Ed.). Autism and Asperger syndrome. Cambridge University Press, Cambridge. pp. 93 - 121.

Wing L. & Gould, J. (1979). Severe impairments of social interaction and associated abnormalities in children. Epidemiology and classification. Journal of Autism and Developmental Disorders, 9: 11 - 29.

Witelson, S.F. (1989). Hand and sex differences in the isthmus and genu of the human corpus callosum: A postmortem morphological study. Brain, 112: 799 - 835.

Witelson, S.F. & Kigar, D.L. (1992). Sylvian fissure morphology and asymmetry in men and women: Bilateral differences in relation to handedness in men. The Journal of Comparative Neurology, 323: 326 - 340.

Woods, R.P., Cherry, S.R. & Mazziotta, J.C. (1992). Rapid automated algorithm for aligning and reslicing PET images. Journal of Computer Assisted Tomography, 16: 620 - 633.

Woods, R.P. (1996). Modeling for intergroups comparisons of imaging data. Neuroimage, 4: S84-S94.

Yirmiya, N., Sigman, M., Kasari, C. & Mundy, P. (1992). Empathy and cognition in high functioning children with autism. Child Development, 63: 150 - 160.

Young, R.L. & Nettelbeck, T. (1995). The abilities of a musical savant and his family. Journal of Autism and Developmental Disorders, 25: 231 - 248.

Zarfas, D.E. & Wolf, L.C. (1979). Maternal age patterns and the incidence of Down's syndrome. American Journal of Mental Deficiency, 83: 353 - 359.

Zatorre, R.J, Evans, A.C., Meyer, E. & Gjedde, A. (1992). Lateralization of phonetic and pitch discrimination in speech processing. Science, 256: 846 - 849.

Zilbovicius, M., Garreau, B., Samson, Y., Remy, P., Barthelemy, C., Syrota, A. & Lelord, G. (1995). Delayed maturation of the frontal cortex in childhood autism. American Journal of Psychiatry, 152: 248 - 252.