The amygdala and social cognitive impairment

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I declare that the work presented in this thesis is my own.

Name __________________________

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Date 13/04/2006 ___________________
ABSTRACT

This thesis investigated the role of the amygdala in social cognition by examining variability in social-perceptual abilities within the normal population and via experiments with individuals who have Asperger’s syndrome (AS).

I found that a significant proportion of men from the general population had a fear recognition deficit akin to that seen in patients with bilateral amygdala lesion and that poor fear recognition was associated with poor theory of mind ability and with reduced activation of the amygdala and associated areas of the ‘social brain’. Further experiments suggested a mechanism for these impairments - reduced fixation of the eye region of the face – similar to that exhibited by patient SM, who has suffered bilateral amygdala damage.

Overall, I found that AS subjects also had a fear recognition deficit when compared with matched controls. However, there was great variability in responses, with scores ranging from normal to severely impaired. Again, an eyetracking experiment showed that low fear recognition was related to a reduced amount of time spent fixating the eyes. Informed by recent neurodevelopmental models of amygdala involvement in autistic-spectrum disorders, I conducted psychological, neurophysiological and neuroanatomical experiments in order to examine the cause of this failure to attend to the eyes in some AS subjects. As a whole, the findings support a ‘hyper-active amygdala model’, in which social stimuli induce an aversive level of arousal and so are avoided. I suggest that inattention to social stimuli, which could have a number of possible aetiologies, might be at the heart of a general route to social cognitive impairment, which could be shared by several distinct populations.
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Chapter 1 - Introduction

The architecture of the mind and brain – modules

The idea that the mind is organised into modules, splitting cognitive processes into smaller, somewhat independent and specialised sub-processes, has been central to cognitive science almost since the inception of the discipline. Marr considered it to be so important that he was moved to “elevate it to a principle, the principle of modular design” (Marr, 1982, pg. 102). There is considerable evidence that a modular design of the mind is to some degree reflected in the neural architecture of the brain. For example, focal brain damage can result in impairments within specific perceptual categories or subtypes of cognitive process. Damage to the amygdala, for instance, prevents fear conditioning despite the fact that subjects retain declarative knowledge of the conditioned-unconditioned stimulus contingencies, whereas hippocampal lesion produces the opposite effect (Bechara et al., 1995). Such ‘double dissociations’ bolster the claim that different neural systems support different computational sub-specialisations.

There is currently much debate over the nature of modularity, a full treatment of which is beyond the scope of this thesis. What, for example, are the necessary criteria for an area of cognition to be considered a module (Coltheart, 1999)? Even more hotly debated are the processes by which modularity comes about: to what extent are modules in the adult mind or brain genetically determined and to what extent do they emerge through patterns of developmental experience (Geary and Huffman, 2002)? Whatever the outcome of these arguments, it seems clear that cognition is often split into sub-processes, implemented by neural systems evolved to be somewhat specialised in their particular brand of information processing.
Evolution, social cognition and the concept of a social cognitive 'module'

From an evolutionary perspective, living in groups is adaptive in that it can provide better security from predators, better mate choice and more access to food. On the other hand, it gives rise to the possibility of within-group competition for resources. One solution to these opposing evolutionary pressures can be seen in the rigid, eusocial behaviour demonstrated by insects, such as ants or bees. Another solution is exemplified by primates, and especially humans, who are imbued with the mental capacity to engage in cooperation and altruism as well as coercion, manipulation and deception. Social cognition refers to the mental processes that make such complex and flexible interactions possible. These include, for example, the ability to recognise a conspecific and their place in one's social network, as well as more complex matters, such as reasoning about the content of other's thoughts, feelings and desires (see Adolphs, 1999a; Adolphs, 2001; Cacioppo et al., 2002 for further discussion).

Given the strong evolutionary pressure, several theorists have suggested that humans have evolved a special purpose cognitive system (i.e. a module) to subserve social behaviour (e.g. Brothers, 1990; Karmiloff-Smith et al., 1995). Following Gardner (1983), behavioural evidence for the existence of a social cognitive module usually takes the form of demonstrating:

a) an evolutionary history to social cognitive abilities, usually via behavioural work with primates

b) the existence of persons with a selective absence of social cognitive ability or, conversely, with spared social cognition in the presence of impairments in other cognitive areas
I will briefly review evidence relating to these factors below.

**Social cognition in primates**

There is a large literature demonstrating sophisticated cognitive processing of social signals by non-human primates (for reviews, see Byrne and Whiten, 1988; Call, 2001; Whiten and Byrne, 1997). For example, there is much evidence that monkeys and apes are able to use information about the direction of a conspecific’s gaze (Emery, 2000). Importantly, studies have shown that gaze following can not simply be explained by low-level mechanisms, such as ‘turn in the direction others are oriented and search until you find something interesting’, as some have suggested (Povinelli and Eddy, 1996). For example, chimpanzees who saw a human experimenter looking above and behind them ignored a distractor object presented to them when they turned around (Tomasello et al., 1999). Furthermore, the same chimpanzees follow gaze around barriers by moving to new locations where their view is unhindered. It seems, therefore, that chimpanzees **understand** that their informants are looking at something specific in a particular location.

Call and colleagues have published a series of studies where a subordinate and a dominate individual compete over two pieces of food placed in a cage, which nicely demonstrate the sophistication of primate social cognition (Hare et al., 2001; Menzel, 1973; Menzel, 1974). Subordinates preferentially approached food that was hidden from the dominates gaze (behind an opaque barrier) but this preference disappeared when the barrier was made transparent – seemingly because they recognised that the transparent barrier was not serving to block the dominant’s visual access to the food. Other experiments showed that subordinates preferentially approached food that dominates had
not seen been hidden, or which had been moved when the dominates were not watching. Finally, when a dominant who had seen the food been hidden was switched for a new dominant who had not, subordinates retrieved more food than they did when the dominant was not switched. Together, these experiments demonstrate that chimpanzees can extract knowledge from their experiences and use it to solve social problems.

However, the precise nature of this knowledge is still uncertain. For example, it may be that non-human primates are able to have insight into the subjective experience of their social partners, that is they may have a theory of mind similar to that of humans (Whiten, 2000). On the other hand, while non-human primates might attribute seeing, wanting and expecting to conspecifics, they may not be able to understand that the belief others hold about things can be different from their own and from reality (Call, 2001). Teasing apart these possibilities will be a difficult task but can potentially provide a fascinating insight into the evolution of our own social-cognitive abilities.

**Selective absence of social cognitive ability – autistic-spectrum disorders**

Autistic-spectrum disorders (ASDs) are pervasive developmental disorders characterised by deficits in communication, the presence of stereotypic or repetitive behaviours and impairments in social interaction (DSM-IV, American Psychiatry Association, 1994). There are three major sub-types: autism, Asperger’s Syndrome (AS) and Pervasive Developmental Disorder Not Otherwise Specified (PD-NOS). AS and autism are differentiated by the lack of a language delay in the former, whereas PD-NOS is reserved for when autistic symptoms are apparent but do not meet the full criteria for the other categories. The shared phenotype of the sub-types of ASDs suggests common
neurobiological and genetic mechanisms (Schultz et al., 2000b; Volkmar et al., 2004) and it is common for them to be considered as one.

Of the three areas of difficulty apparent in ASD, deficits in social cognition are generally considered to be the most definitive and compelling (Grelotti et al., 2002). Individuals with an ASD have significant difficulty with social interactions; they can be somewhat unaware of social norms and have difficulties establishing social relationships with others (Volkmar et al., 1994). Crucially for the argument of a social cognitive ‘module’, these impairments can be demonstrated in the absence of a general cognitive deficit.

One prominent psychological account of ASD is that those with the condition lack a ‘theory of mind”, that is, the capacity for conceiving of other people’s and one’s own mind (Baron-Cohen et al., 1985). Individuals with an ASD have difficulty in making attributions of mental states to others and to themselves, thought to result in an inability to construct a social world that is guided by intentions, desires and beliefs (for review, see Baron-Cohen et al., 2000b).

Affected individuals show deficits on a myriad of tasks which tap into social-perceptual and social-cognitive abilities (Cohen and Volkmar, 1997). Of these, problems with face processing are particularly pervasive (Grelotti et al., 2002). Failure to make eye contact and inattention to faces were noted in Kanner’s (1943) original description of the disorder. Modern eye-tracking equipment has confirmed that adults with an ASD fixate the face, and particularly the eye region, less than do normal controls (Dalton et al., 2005; Klin et al., 2002; Pelphrey et al., 2002). These abnormalities are present from an early age: in a retrospective study of the first birthday parties of 11 children with autism and 11 typically developing controls, the children with autism showed significantly less interest in the
faces of other people, as well as being less likely to show objects to other people or to orient to someone calling their name (Osterling and Dawson, 1994). Individuals with an ASD appear to perceive faces in a feature-based rather than a configural manner, shown for example by their failure to demonstrate an ‘inversion effect’ (Hobson et al., 1988b; Langdell, 1978). As configural processing of a stimulus is associated with experience and expertise, autistics are sometimes considered to be face ‘in-experts’ (Grelotti et al., 2002). There are reports that those with an ASD are poor at recognising emotion from faces (Hobson et al., 1988a; Hobson et al., 1989) and that this might be specific to negative emotions such as fear (Howard et al., 2000; Pelphrey et al., 2002). However, this remains a controversial issue with a number of negative findings (Castelli, 2005; Ozonoff et al., 1990). The emotion recognition deficits seen in ASD and their implication for neurocognitive models of social cognition are explored in more depth in a later section.

**Selective sparing of social cognitive ability – Williams syndrome**

Williams syndrome is caused by a deletion of a set of genes on chromosome 7 and results in an unusual facial morphology, heart abnormalities and an intriguing cognitive profile (see Bellugi and St George, 2000, for review). Although the subjects have generally low IQ and are severely impaired in visuospatial processing, they appear remarkably able socially (Karmiloff-Smith et al., 1995). They are able to perform many social tasks, including linguistic ones, normally and in fact often appear *hypersocial* in terms of their interaction with adults. Many suggest the disease provides something close to the converse of ASD (Bellugi and St George, 2000) and is therefore considered to be an example of selective sparing of social cognitive ability in the presence of deficits in other areas of cognition.
Summary

The evidence discussed in this section demonstrates an evolutionary history to human social cognitive ability and provides examples of persons with both a selective absence of social cognitive ability and spared ability in the presence of other cognitive impairments. There is therefore converging support for the notion of a social cognitive module of the mind. The next section explores how this module may be implemented within the neural architecture of the brain.

The neurobiology of social cognition

It has long been supposed that the social cognitive module is embodied in a network of brain regions, specialised for processing social information. In her seminal review, Brothers (1990) draws mainly upon work on single cell recordings in non-human primates to outline such a network, consisting of the amygdala, temporal cortex and anterior cingulate cortex. To this she later adds the orbitofrontal cortex (Brothers, 1997). In the years since, this model has been built upon and refined (for reviews, see Adolphs, 1999a; Adolphs, 2001). In most constructs the model consists of areas thought to identify (perceive) socially relevant stimuli, such as faces or emotional expressions (e.g. the fusiform gyrus and the superior temporal gyrus), areas to attach emotional, social or motivational significance to such stimuli (e.g. the amygdala) and areas believed to engage in social reasoning (e.g. the prefrontal cortex). Recent work has added the concept of a specific “theory of mind” network, specialised for understanding the mental states of others (Gallagher and Frith, 2003), as well as the idea of a mirror neuron system, aiding the understanding of other’s behaviour through simulation (Blakemore and Frith, 2005). Below, I will briefly review the evidence linking each area of this network to social cognition.
**Fusiform cortex**

Numerous neuroimaging studies have found that an area of the fusiform cortex responds to faces more than to visual stimuli of other categories (e.g. Kanwisher et al., 1997; McCarthy et al., 1997). Although there is a debate regarding the degree to which this area of cortex is specifically specialised for face perception (Kanwisher, 2000; Tarr and Gauthier, 2000), the robustness of the effect is such that the area has become known as the ‘fusiform face area’ (FFA). Experiments that vary which properties of the face are attended to (Hoffman and Haxby, 2000), or examine which neural areas show adaptation when a stimulus property is repeated (Gauthier et al., 2000; Winston et al., 2004), suggest that the FFA analyses the identity of the person to which the face belongs.

**Superior temporal sulcus and surrounding cortex**

The area comprising of the superior temporal sulcus (STS) and surrounding gyri was first thought to have a role in social cognition following electrophysiological recordings in non-human primates, which found single neurons responsive, in a relatively selective manner, to faces (e.g. Perrett et al., 1982). Further work found cells in monkey STS responsive to head or gaze direction (Perrett et al., 1985b) and to body (Perrett et al., 1985a), and even specific hand, movements (Perrett et al., 1986).

In humans, neuroimaging studies have found analogous regions to be involved in processing gaze direction (Calder et al., 2002; Hoffman and Haxby, 2000) as well as biological motion: including body movements (Bonda et al., 1996; Grossman and Blake, 2001; Senior et al., 2000), hand movements (Grezes et al., 1999; Grezes and Costes, 1998) and mouth movements (Calvert et al., 1997; Puce et al., 1998). This is true even when the movement is relatively abstract, as in the case of point light displays (Bonda et al., 1997; Puce et al., 1998).
of enactment by geometrical shapes imitating purposeful movement (Schultz et al., 2003) and when movement is merely implied, as in a static image of a moving person (Kourtzi and Kanwisher, 2000). In addition, the STS has often been shown to be responsive to the emotional expression of faces (e.g. Narumoto et al., 2001; Winston et al., 2003a; Winston et al., 2004).

Together, these findings suggest the STS has a primary role in the initial perception and analysis of visual social cues. However, recent work has shown an even broader role for the human STS – namely in the process of ‘mentalizing’ whereby one infers the beliefs, feelings or intentions of others. For example, Gallagher et al. (2000) found STS activity to be associated with understanding the meaning of stories or cartoons. Other neuroimaging experiments using theory of mind tasks have found STS activity when people attribute intentions to the movements of geometric shapes (Castelli et al., 2000) or when taking the self-perspective (Vogeley et al., 2001). Incorporating the latter findings, Frith and Frith (1999) suggest that the STS is involved in the detection of the behaviour of agents and the analysis of the goals and outcomes of this behaviour.

**Anterior superior temporal sulcus and gyrus**

In general, the neuroimaging studies described above report activation confined to the posterior two-thirds of the STS and surrounding gyri (see Gallagher and Frith, 2003; and Puce and Perrett, 2003, figure 3). However, the role of the anterior third of this area (or, at least, of the superior temporal gyrus, roughly BA 22) has been implicated in social cognition by two recent neuroimaging studies. Both Calder et al. (2002) and Wicker et al. (2003) found activation in the anterior superior temporal gyrus (STGa) when they compared direct to averted gaze. Furthermore, the data reported by Wicker et al. (2002)
suggests that the STGa may be selectively involved in the reading of emotion from the eyes when focussed directly on the viewer.

**Amygdala**

The amygdala has long been associated with social and emotional processing (Adolphs, 1999b). Recent theories stress its role as a ‘salience detector’: monitoring sensory input for stimuli of high emotional or social relevance (e.g. Sander et al., 2003). Thus, in terms of the social brain network, the amygdala is thought to apply emotional significance to social stimuli perceived by, for example, the FFA and STS (e.g. Adolphs, 2001). The amygdala is then thought to be able to modulate attention, memory and reasoning, thus influencing current and future behaviour in light of the salient stimulus (Dolan, 2002).

The role of the amygdala in social cognition is central to this thesis and will be considered in depth in subsequent sections.

**Temporal poles**

In primates, the temporal poles are generally associated with object and face recognition (Nakamura and Kubota, 1996). However, in humans, neuroimaging experiments have activated these regions during tasks requiring retrieval of episodic memories. For example, the temporal poles are active during the recollection of familiar faces and scenes (Nakamura et al., 2000), the recognition of familiar voices (Nakamura et al., 2001), autobiographical memory retrieval (Fink et al., 1996) and emotional memory retrieval (Dolan et al., 2000). Furthermore, the temporal poles are one of a number of regions consistently activated in theory of mind reasoning (Gallagher and Frith, 2003). On the
basis of these data, Gallagher and Frith (2003) suggest that the temporal poles are a store for semantic and episodic memories and are engaged in this regard during mentalizing (where, for example, memory of past interactions could aid in an analysis of someone's current intentions). Interestingly, in an fMRI study by Kampe et al. (2003) subjects activated the temporal poles both when someone looked directly at them and when their name was called, suggesting this region is also involved in processing signals of communicative intent.

**Prefrontal cortices**

The famous case of Phineas Gage first highlighted the role of the prefrontal cortex in social cognition (Damasio et al., 1994). Previously a polite, socially adept person, Gage changed dramatically following damage to his frontal lobe, becoming uncaring, profane and socially inappropriate. Studies by Damasio and colleagues (Damasio, 1994; Eslinger and Damasio, 1985) have confirmed this finding and pinpointed the orbitofrontal cortex as being crucial to adaptive social functioning. Patients with damage to this region demonstrate a diminished capacity to respond to punishment, stereotyped and occasionally inappropriate social manners and a lack of concern for others. Early orbitofrontal damage can impair social and moral reasoning later in life (Anderson et al., 1999), which is consistent with neuroimaging findings that show this area to be active when subjects make moral judgments (Moll et al., 2002a; Moll et al., 2002b).

An area of medial prefrontal cortex (more accurately, the anterior paracingulate cortex), roughly corresponding to Brodmann area 9 or 32, is considered play a major part in the so called 'theory of mind network (see below). Not only is it consistently active in neuroimaging studies using theory of mind tasks but it appears to be the only part of this
network that is activated specifically to mentalising (Gallagher and Frith, 2003). Furthermore, two well-controlled experiments, in which the only difference between the mentalising and control conditions was the subject’s belief about whether they were playing a human or computer, found activation only in the anterior paracingulate cortex (Gallagher et al., 2002; McCabe et al., 2001).

The theory of mind network

As alluded to above, three regions have consistently been associated with theory of mind processing during neuroimaging studies, namely: the anterior paracingulate gyrus, the superior temporal sulcus and the temporal poles. In a series of reviews, Frith and colleagues (Frith and Frith, 1999; Frith, 2001; Gallagher and Frith, 2003) have suggested specific roles for each of these areas within a dedicated theory of mind network. The anterior paracingulate gyrus is seen as the key region for mentalising; it is the centre of the reasoning needed to determine an agent’s mental state. The other two regions of the network are thought to aid in this process by providing information relevant to the reasoning – the STS analyses cues from an agent’s body movements or changing facial features, while the temporal poles provide relevant memories of past social encounters.

It should be noted that, as yet, the evidence for this network as a ‘mentalising system’ is based almost entirely on neuroimaging findings. Lesion and other studies are sparse. In fact, a lesion study has shown that extensive damage to the anterior paracingulate gyrus does not necessarily result in impairments on theory of mind tasks (Bird et al., 2004).
The mirror neuron system

The pre-motor areas of non-human primates have been shown to have so called ‘mirror neurons’, cells which respond both when a monkey performs an action and when that monkey observes the same action by another (Gallese et al., 1996; Rizzolatti et al., 1996). Neuroimaging studies have provided evidence of analogous activity in human premotor regions and it has been suggested that such activity could represent an attempt to understand and predict another’s actions through simulation of the neural processing that would be required to perform those actions (Blakemore and Frith, 2005). This notion of understanding through simulation has been extended to the social and emotional domains, where it is linked with the somatosensory regions (Adolphs, 1999a; Adolphs, 2001). For example, damage within the right somatosensory cortices impairs the judgment of other people’s emotional states from their faces (Adolphs et al., 2000a). In particular, lesion and neuroimaging studies converge to implicate the insula in both the experience and recognition of disgust (e.g. Calder et al., 2000; Wright et al., 2004).

Social cognitive stimuli

The key sensory channels used by most mammals for social communication are olfaction and touch: rat mothers, for example, recognise their pups by smell (Hauser and Konishi, 1996). In most primates, however, it is the visual system that is most commonly involved in the perception of social stimuli. Some authors even suggest that the increased reliance on visual signals in primates has been driven by increases in the sophistication of social interactions. When it comes to complex interactions involving, for example, deception or cooperation, it is proposed that visual signals offer evolutionary advantages over the other modalities in that they can be directed to specific individuals and suffer less from ambiguity (see Emery, 2000, for further discussion).
For primates (especially humans), few visual signals carry a greater abundance of social information than the face (Adolphs, 2001). From an individual’s face it is possible to ascertain their identity, age, gender, emotional state and the direction of their attention. Such information is critical to inferring another’s mental state or intentions (Baron-Cohen, 1995). Therefore, it is no surprise that laboratory investigations into human (and primate) social cognition have largely focussed on aspects of face perception, including memory for faces (Broks et al., 1998), analysis of eye gaze direction (Elgar et al., 2002; Leekam et al., 1997), assessment of sexual attractiveness (Perrett et al., 1994; Perrett et al., 1998), assessment of trustworthiness from the face (Adolphs, 2002; Winston et al., 2002) and the perception of emotional expressions (Blair, 2003; Russell et al., 2003). Of the facial features, the eyes have received much attention (Emery, 2000). Direct gaze is an extremely potent social stimulus, potentially signalling threat, sexual desire or simply the desire to communicate (Kampe et al., 2003). Averted gaze can signal the focus of an individual’s attention and as such can be an important cue to understanding his intentions (Bruinsma et al., 2004; Phillips et al., 2002). Both the perception of emotional expressions and the importance of eyes as a transmitter of social information are fundamental to this thesis and are considered in greater depth in the following two sections.

Facial expressions of emotion

The facial musculature is far more developed in primate compared to non-primate animals (Andrew, 1963), allowing primates, especially humans, to produce a wide-range of facial expressions of emotion. Six of these (happiness, sadness, fear, surprise, anger and disgust) have been shown to be consistently produced and recognised across cultures, even amongst isolated peoples, such as the Dani of West New Guinea (Ekman and Friesen, 1971; Izard, 1971). Evidence of this kind has led some to suggest that these six
'basic' emotions might be universal and innate (Ekman, 1994; Izard, 1994). However, this belief is still contested (Russell, 1994). Whatever the outcome of this debate, it seems certain that in all cultures facial expressions are key providers of the signals necessary for social interaction.

The analysis of facial expressions by muscle contractions began with the electrophysiological work of Duchenne (1862/1990). This was later expanded on by Darwin (1872/1998) and formalised by Ekman and Friesen (1978) in their Facial Action Coding System (FACS). FACS identifies the presence of specific actions of facial muscles (action units) in emotional expressions and is therefore able to characterise each emotion by the muscle contractions that are typically involved.¹

However, not all features of an emotional expression are used equally when a person attempts to infer what another is feeling. In an elegant study, Smith et al. (2005) characterise the information underlying the recognition of the six basic emotional expressions using the 'Bubbles' procedure (Gosselin and Schyns, 2001). In this task, subjects view sparse images of faces, in which only a random sub-set of features are revealed in any one stimulus presentation, and attempt to categorise the underlying emotional expression. From the results it is possible to define the information that is most often used to classify each expression – see figure 1. Interestingly, where there is

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¹ An important idea, first touched on by Duchenne (1862/1990) and Darwin (1872/1998) but later expanded on by Ekman and colleagues (Ekman et al., 1990; Frank et al., 1993), concerns the fact that some muscle contractions involved in a facial expression are voluntary while some are not. This has implications for deception and communication in that there exist subtle but consistent differences between faked and real expressions of emotion. To take a famous example - a heart-felt smile involves contraction of the orbicularis oculi muscles, which are not under voluntary control, producing characteristic wrinkles around the eyes - the so-called Duchenne smile. The social, or fake, smile on the other hand, lacks the orbicularis oculi contraction and the corresponding eye-wrinkling. From an evolutionary perspective, it would make sense for us to have become highly tuned to those aspects of a facial expression that are involuntary, enabling us to spot with ease when an expression is real and when it is fake. However, evidence that we do indeed possess this skill is thin on the ground, limited at present to a modest ability to recognise 'Duchenne' compared to faked smiles (Frank et al., 1993).
ambiguity between the information transmitted from a face stimulus, the human ‘information seeking strategy’, serves to minimise this ambiguity. This is relevant for differentiating between surprised and fearful expressions, the typical features of which overlap to a high degree: information from the mouth and from the eyes characterise both emotions. To solve this ambiguity, human observers appear to rely on information from the eyes for fearful faces and from the mouth for surprised faces (see figure 1). Smith et al. (2005) see this as an example of the brain’s decoding structures seeking to orthogonalize dissimilar inputs. A failure of this optimal information seeking strategy may be relevant to the emotion recognition deficits seen in some psychiatric populations, who often mis-label “fearful” expressions as “surprised”. This issue will be discussed in more detail in subsequent sections.

Disorders affecting social cognition often produce deficits in labelling the six basic emotional expressions. Schizophrenics, for example, reliably show such deficits, although the precise manifestation of the impairment is inconsistent (for review see, Edwards et al., 2002). Specific deficits in fear recognition have been reported in autism (Howard et al., 2000; Pelphrey et al., 2002), Turner Syndrome (Lawrence et al., 2003) and psychopathy (Blair et al., 2004; Dadds et al., in press). These findings have been received with a great
deal of interest, largely because fear recognition has been strongly linked to amygdala function both in lesion (Adolphs et al., 1999; Calder et al., 1996) and neuroimaging studies (Breiter et al., 1996; Morris et al., 1996). The link between the amygdala and processing of fearful faces is given more detailed consideration in a later section.

The importance of eyes for social cognition

Many vertebrate species have evolved a system for detecting eyes, which seems to serve the function of a rapid, predator detector (Emery, 2000). For example, lesser mouse lemurs engage in greater gaze aversion when shown two schematic eyes presented horizontally compared to the same stimuli presented vertically (Coss, 1978). Similar results have been found for certain species of birds (Jones, 1980; Scaife, 1976), house mice (Topal and Csanyi, 1994) and jewelfish (Coss, 1979). A number of species are also able to ascertain whether a pair of eyes are fixed upon them or away from them, which has obvious evolutionary value in terms of avoiding predators (see Emery, 2000, for further examples).

However primates, especially humans, utilise the eyes to a far greater degree, using them for complex communicative functions. For example, by analysing the direction of a conspecific’s gaze it is possible to infer what they are attending to and why it has significance. Such ‘allocentric’ gaze monitoring is thus critical for the development of joint attention, an ability thought to be a pre-cursor to theory of mind and known to be impaired in children with autism (Charman, 2003; Leekam et al., 2000).

In addition, direct eye-contact is highly relevant for human social communication (Kleinke, 1986) and can indicate signals as diverse as threat and sexual attraction. The
ability to distinguish direct from averted gaze is present in the newborn (Batki et al., 2000; Farroni et al., 2002) and by later life has become highly sensitive (Senju et al., 2003; von Grunau and Anston, 1995). Consistent with this, direct gaze activates the amygdala (Kawashima et al., 1999) and enhances FFA activity, an effect which can be attributed to amygdala-fusiform modulation (George et al., 2001). Furthermore, the fact that direct gaze activates the theory of mind network (Calder et al., 2002; Kampe et al., 2003), demonstrates that eye contact is a socially significant stimulus, initiating immediate analysis of the intentions of the onlooker.

Consistent with the importance of the eyes as conveyors of social signals, when scanning faces humans reliably spend most time fixating on the eye-region (Adolphs et al., 2005; Horley et al., 2004; Mertens et al., 1993; Pelphrey et al., 2002; Walkersmith et al., 1977). This pattern has been demonstrated in children as young as five weeks old (Haith, 1977) as well as non-human primates (Keating and Keating, 1982; Nahm et al., 1997).

**The eyes are especially important for recognising fearful expressions**

Traditionally, the eyes have been thought of as key communicators of emotion – in literature, eyes are referred to as the “windows of the soul” (Du Bartas)\(^2\), that “are often voice and words in a silent look” (Ovid)\(^2\). Baron-Cohen (1997b) has argued for a “language of the eyes” and has shown that, at least for complex, subtle feelings such as guilt or admiration, the eyes are critical for accurate emotion recognition. For the basic emotions however, the eyes appear to be less crucial (Baron-Cohen et al., 1997b) – except, that is, for fearful expressions. The study by Smith et al. (2005), described above,

\(^2\) Taken from (Stevenson, 1967).
clearly shows the heavy reliance that humans place on information from the eyes in order to recognise fearful faces (see figure 1). This finding is confirmed by Kohler et al. (2004) who, using the FACS system, analysed which action units of emotional expressions are most associated with correct recognition of the given emotion. For fearful faces, it was nostril dilation (which occurred infrequently) and widened eyes.

Neuroimaging studies confirm the importance of the eyes for fearful expressions. Using chimerical stimuli (fearful eyes with a neutral mouth compared to neutral eyes with a fearful mouth), Morris et al. (2002) showed that the eyes are critical for producing the well documented amygdala response to fearful faces (Breiter et al., 1996; Morris et al., 1996; Winston et al., 2003a). Whalen et al. (2004) show that even isolated fearful eyes, removed from the context of the face, produce amygdala activation in comparison to neutral eyes. Furthermore, it appears to be the presence of a large white area (the sclera) surrounding a black circle (the pupil), rather than the shape of the fearful eyes, which drives the amygdala response: eye images with the colours inversed produced no amygdala activation.

Recent work with the amygdala-lesioned patient, SM, further supports the importance of the eyes for recognising fear (Adolphs et al., 2005). SM has a well circumscribed, bilateral lesion of the amygdala, which is thought to have resulted in a severe and selective impairment in the recognition of fear from facial expressions (Adolphs et al., 1994; Adolphs and Tranel, 2000). Importantly, this is in the absence of any impairment in perception, memory, language and reasoning - in so far as these do not involve the processing of emotional stimuli (Adolphs and Tranel, 2000). Using the Bubbles task, Adolphs et al. (2005) show that, unlike normal controls, SM fails to make use of visual information from the eyes in faces (see figure 2a). Furthermore, when scanning complete
face stimuli, SM fails to explore the face normally and, in particular, spends significantly less time fixating the eyes compared to normal controls (see figure 2b). These abnormalities are present for all face stimuli – not just for fearful expressions. However, Adolph's et al (2005) propose that they manifest as a specific fear recognition impairment because it is only for this basic emotion that information from the eyes forms a vital component. Such an explanation fits well with reports of SM's other impairments, notably a failure to read complex 'social' emotions (Adolphs et al., 2002), a skill which Baron-Cohen et al. (1997b) has shown relies critically on reading information from the eyes.

A number of other populations show similar abnormalities to SM. Psychopathic individuals, for example, have a specific fear recognition deficit (Blair et al., 2004; Dadds et al., in press), which is shown to be temporarily corrected by asking them to focus on...
the eye region of faces (Dadds et al., in press). With increasing age, otherwise healthy adults show a progressive reduction in the ability to recognise fear and, to a lesser extent, anger and sadness (Calder et al., 2003; Malatesta et al., 1987; Wong et al., 2005). This has been associated with an increasingly abnormal scan pattern with progressing age: older adults spend less time fixating on the upper half of the face, focussing more on the lower half (Wong et al., 2005).

With one exception (van der Geest et al., 2002), people with an autistic-spectrum disorder have consistently been shown to spend less time fixating the eyes in pictures of faces (Dalton et al., 2005; Klin et al., 2002; Klin et al., 2003; Nacewicz et al., 2006; Pelphrey et al., 2002). In addition, there is some evidence that those with an ASD may have a fear recognition deficit (Howard et al., 2000; Pelphrey et al., 2002), but this remains controversial and there are a number of negative findings (Adolphs et al., 2001; Castelli, 2005). This research is reviewed in more detail in a subsequent section.

In ASD, the studies examining abnormal scanpath and impaired emotion recognition have remained essentially separate lines of inquiry: as yet, no one has formally investigated the links between the two. Given the strong connection between eye fixation and fear recognition (discussed above) and given the consistent evidence of poor fixation of the eye region in ASD, one would predict that a fear recognition deficit in ASD would be easy to demonstrate. Why this is not the case and, furthermore, the reasons why people with ASD should fixate less on the eyes than normal controls have not been empirically explored. Experiments attempting to shed light on these issues are presented in chapters 4 and 5.
Theory of mind tasks

The original test of the ability to attribute thoughts and feeling to others is the ‘false belief task’ in which a subject must keep track of a character’s mistaken mental state in order to predict how the character will behave based on that belief (in contrast to the subject’s own belief or reality). False belief tasks can be first order (‘she thinks X’), such as the Sally-Anne test (Baron-Cohen et al., 1985), or the more difficult second order (‘she thinks that he thinks X’), such as the Ice-Cream story (Perner and Wimmer, 1985). Such tasks have been a useful starting point for tracking the theory of mind deficits in children with an ASD. However, they have a number of limitations. Firstly, they call upon mental faculties other than ToM, such as executive function, with which children with autism have been shown to be impaired (Russell, 1998). Secondly, higher-functioning children and adults with ASD, particularly those with AS, are able to pass false belief tasks despite a continuing, real-world failure to understand what other’s think and feel (Frith et al., 1994).

To combat these restrictions, researchers have attempted to develop tasks which assess ToM reasoning in relative isolation and/or highlight the difficulties faced by higher-functioning ASD individuals. One of the latter ‘advanced’ ToM tasks is based on Baron-Cohen’s (1997b) work into the ‘language of the eyes’: subjects have to recognise complex social emotions using the eyes alone (Baron-Cohen et al., 1997a). This, however, confounds social-perceptual ability with ToM reasoning. Another approach asks subjects to infer character’s thoughts and feelings from a verbal story (Happe, 1994). However, Abell et al. (2000), have created a ToM task (known as the Happé-Frith triangles task), which is divorced from the human context. This is based on the observations of Heider and Simmel (1944) that, when shown silent animations of a triangle and a circle moving
within a rectangle, adults were inclined to describe the events in terms of intentional action. Abell et al. (2000) created animations in which geometrical shapes engaged in goal-directed sequences (e.g. chasing) or in ToM related sequences (e.g. tricking). Both children (Abell et al., 2000) and adults (Castelli et al., 2002) with high-functioning autism or AS made fewer and less appropriate mental state attributions to the ToM sequences. Furthermore, in fMRI normal adults activate areas of the ToM network (namely the posterior STS, medial prefrontal cortex and temporal poles) when viewing the ToM cartoons, while those with an ASD do not (Castelli et al., 2000; Castelli et al., 2002). I use the Happé-Frith triangles task in chapter 3 to assess the ToM abilities of healthy adults with a fear recognition deficit.

The amygdala and emotion

There is a vast literature linking the amygdala to the processing of emotional stimuli (for review see, Dolan, 2002; Phelps, 2006; Phelps and Le Doux, 2005). A very brief overview of this large topic will be given here, including some ideas regarding the amygdala’s function in moment-to-moment behaviour. I will then move on to the more germane topic of the amygdala’s role in social cognition.

Implicit emotional memory – fear conditioning

Much research, mostly conducted in rodents but confirmed to some extent in humans, has identified the amygdala as the central structure in the acquisition and expression of fear conditioned memories (for review see, LeDoux, 1996; Ledoux, 2000; Maren, 2001). Based on work with rats, the lateral nucleus (LA) is typically viewed as the sensory interface of the amygdala and as the key site of plasticity, while the central nucleus (CE) is viewed as
the output region. LA receives inputs from sensory thalamus as well as from cortical sensory areas. The thalamic input is seen as a quick, but crude, route to the amygdala, whereas the cortical input provides a slower but more fine-grained representation (LeDoux, 1996; LeDoux, 2003). The functional significance of these two pathways is considered later. CE controls the expression of fear responses via projections to various subcortical nuclei, such as the hypothalamus (blood pressure changes, stress hormone release) and central grey (freezing behaviour), (LeDoux, 1996; Ledoux, 2000; Maren, 2001).

Brain imaging studies with humans are consistent with this animal model. In fMRI, the amygdala is activated during fear conditioning (Buchel et al., 1998; Labar et al., 1998) and the magnitude of this activity is correlated with the strength of the conditioned response (Labar et al., 1998). Furthermore, a CS presented subliminally leads to co-activation between the amygdala and both the superior colliculus and pulvinar (Morris et al., 1998b). These structures are thought to be components of a subcortical route to the amygdala, consistent with the data showing both a cortical and a subcortical pathway to the amygdala in the rat.

Finally, data from patients with brain damage are also consistent with the animal model. Damage restricted to the amygdala prevents the acquisition and/or physiological expression of conditioned fear, despite having no effect on the explicit memory of the conditioning procedure. Patients with hippocampal damage, on the other hand, demonstrate the physiological expression of conditioned fear but have no conscious recollection of being conditioned (Bechara et al., 1995).
Emotional modulation of memory

The amygdala appears able to modulate memory consolidation in other brain regions, notably the hippocampus, thereby enhancing memory for emotionally arousing events (McGaugh, 2000). This is indicated by studies in rats where post-training, neurochemical knockout of the amygdala prevents normal enhancement of memory for a fear-arousing event (LeDoux, 2003). In humans, damage to the amygdala impairs memory for emotional stimuli (Adolphs et al., 2000b; Cahill et al., 1995) and, in fMRI, activation of the amygdala during encoding is predictive of later memory retention for emotional stimuli (Cahill et al., 1996; Canli et al., 2000; Dolcos et al., 2004; Hamann et al., 1999).

Emotional modulation of attention and perception

It is of obvious evolutionary value for an unattended, but emotionally important, stimulus to gain rapid access to awareness. An influential idea is that this is achieved by amygdala modulation of other brain areas (Armony and LeDoux, 1999; Dolan, 2002): the amygdala detects the salient stimulus (rapidly, possibly via the subcortical route) and facilitates attention and perception towards that stimulus via feedback projections to sensory cortex (Amaral et al., 2003b; Freese and Amaral, 2005).

In support of this, patients with amygdala damage do not show the normal facilitation of attention for emotional stimuli, as demonstrated in an attentional blink paradigm (Anderson and Phelps, 2002). Neuroimaging experiments have shown enhanced activation of fusiform cortex to emotionally arousing (i.e. fearful) rather than to neutral faces and this is correlated with amygdala activation (Morris et al., 1998a; Morris et al., 1998b). This facilitation of cortical sensory processing is absent if the amygdala is damaged (Vuilleumier et al., 2004).
These lesions and neuroimaging studies provide strong support for the idea that the amygdala modulates attention and perception via feedback to sensory cortex. In order for this modulation to be effective, the amygdala must receive and process information about the relevant stimulus before it has been processed in the region to be modulated. Achieving this early amygdala input is thought to be the function of the ‘quick and coarse’ subcortical route to the amygdala – possibly via the superior colliculus and pulvinar (Morris et al., 1999). In support of this, the amygdala can differentiate between fearful and neutral faces even when these are presented unconsciously (Morris et al., 1999; Pasley et al., 2004; Whalen et al., 1998; Williams et al., 2004). In addition, Vuilleumier et al. (2003) took advantage of the fact that a subcortical visual pathway would be more sensitive to low-frequency spatial information, whereas a cortical route would be tuned to high-spatial frequencies. They found that the superior colliculus, pulvinar and amygdala responded preferentially to low-spatial frequency fear versus neutral faces. Furthermore, by using hybrid high- and low-spatial frequency faces, Winston et al. (2003b) showed that enhancement of fusiform activity to fearful faces is driven by low-spatial frequency information (to which the fusiform is not preferentially tuned). Finally, subjects with damaged visual cortices (so called ‘blindsight’ patients) can show differential amygdala activity to fearful and neutral faces, despite being unable to consciously perceive the stimuli (Morris et al., 2001; Pegna et al., 2005).

The amygdala as a ‘salience detector’ – modulating current and future behaviour

The majority of research on the amygdala has focussed on its reactivity to negatively valenced (often fear related) stimuli, resulting in it being viewed as part of a fear- or danger-specialised cognitive module (Ohman and Mineka, 2001; Paradiso et al., 1999).
However, this has been challenged by findings that the amygdala is activated by positive events, such as happy faces (Canli et al., 2002; Winston et al., 2003a; Yang et al., 2002), positive words (Hamann and Mao, 2002), pleasant tastes (O'Doherty et al., 2001) or erotic film excerpts (Karama et al., 2002; Redoute et al., 2000). Two theoretically important studies, using olfactory (Anderson et al., 2003) and gustatory (Small et al., 2003) stimuli, demonstrate that amygdala activity co-varies with the perceived arousal of events, not with the valence. Therefore, more recent theories present the amygdala as a 'salience' or 'relevance' detector (e.g. Dolan, 2002; Sander et al., 2003). The slight bias of the amygdala response towards negatively valenced stimuli is likely to be an example of a system-wide 'negative bias', thought to reflect the fact that potentially dangerous events have become particularly relevant to us through our evolutionary history (Ito et al., 1998)

Once a salient event has been detected, we have seen that the amygdala can associate it with other stimuli that might better predict it (fear conditioning), modulate sensory cortex to enhance its current processing and influence hippocampal activity to facilitate its entry into long term memory. In light of a relevant event, the amygdala is thereby able to influence current and future behaviour, facilitating an adaptive response and assisting in the success of the organism. For social animals, each encounter with a conspecific is replete with potentially relevant stimuli. It is perhaps therefore not surprising that there has been much interest in the amygdala's role in social cognition, which will be discussed in the next section.

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3 According to Sander et al. (2003, pg. 311), an event is relevant to an organism if it, "can significantly influence (positively or negatively) the attainment of his or her goals [or] the satisfaction of his or her needs".
The amygdala and social cognition

Amygdala lesion alters social behaviour in non-human primates and rats

The seminal work of Kluver and Bucy (1937; 1939) first suggested that the amygdala might be involved in social behaviour. This work showed that ablation of the temporal lobes in macaque monkeys caused profound changes in behaviour, including: loss of fear, changes in food preferences, hypersexuality and reduced social interaction. Further work revealed that most of these behavioural changes can be produced following more selective ablations, restricted largely to the amygdala (Aggleton and Passingham, 1981; Weiskrantz, 1956). Later, Bachevalier and colleagues (1994; 2001) found that lesions to the amygdala and surrounding structures in infant monkeys reduces dyadic social interaction later in life, leading to the suggestion that such early lesions might provide an animal model of autism (Bachevalier, 1994). A number of naturalistic observational studies of monkey behaviour following amygdalectomy are consistent with these data (e.g. Dicks et al., 1969; Kling et al., 1970; Kling, 1972). For example, Dicks et al. (1969) retrieved rhesus monkeys from their natural habitat, subjected them to bilateral amygdala ablation and then returned them to their social groups. The lesioned animals failed to integrate socially and often died without support from their troop.

However, Amaral and colleagues have pointed out a number of methodological problems with these studies (Amaral, 2003; Amaral et al., 2003c) and new experiments designed to control for these deficiencies do not fully support the data described above (Bauman et al., 2004a; Bauman et al., 2004b; Emery et al., 2001; Prather et al., 2001). A major shortcoming of the earlier amygdalectomy work was the use of suction or radio frequency
ablation to produce the lesion. Such methods destroy not only the cell bodies in the lesioned area but also damage axons travelling through the targeted brain region. As a result, it is impossible to determine whether the behavioural changes produced following the older lesion methods were due to elimination of the targeted region or to the inadvertent interference with connections between two or more untargeted areas. Another major concern, at least in studies where lesions are produced neonatally, is how the animals are reared. In earlier studies, infant monkeys were reared away from their mothers; however recent evidence suggests that this in itself can produce abnormalities in later social interaction, (Sackett et al., 2002), confounding any lesion effects.

In their recent program of research (Bauman et al., 2004a; Bauman et al., 2004b; Emery et al., 2001; Prather et al., 2001), Amaral and colleagues avoided the confounds of earlier studies by using ibotenic acid to produce neurotoxic lesions, which destroyed only the cell bodies and not the fibres of passage in the region. They also mother-reared subjects and provided daily access to large social groups, thus simulating a natural environment.

In the first of these investigations, Emery et al. (2001) produced bilateral amygdala lesions in adult male rhesus monkeys and observed their behaviour in dyadic social interactions with age, sex and dominance matched control animals. Rather than showing reduced social interaction, the amygdala lesioned animals generated significantly greater amounts of affiliative social behaviour (groom, present sex etc) towards other monkeys than did controls and appeared to be socially uninhibited. The authors conclude that an intact amygdala in not essential for carrying out social behaviour in adult monkeys. Instead, they suggest that the amygdala normally serves to monitor the environment for potential threats. By removing it, the “break” is lifted – the lesioned animals fail to perceive the potential danger of the interaction and so do not apply the species-typical caution usually provoked by such encounters. This conclusion is bolstered by
observations of the lesioned monkeys’ responsiveness to novel, non-social, objects. Monkeys typically exercise caution when faced with such stimuli, yet the lesioned monkeys did not, approaching and tactually exploring the objects. This was true even of normally fear-eliciting stimuli, such as a rubber snake, which a non-lesioned monkey would normally never explore tactually.

While the above data argues against the idea that the amygdala is essential for the production of social behaviour in an adult monkey, it is still possible that the amygdala might be critical for the development of appropriate social interaction. This idea carries weight, as a recent theory of the amygdala’s role in autism stresses a neurodevelopmental perspective (Grelotti et al., 2002; Schultz, 2005) and, in humans, early amygdala lesion causes significantly greater deficits in ToM tasks than do later lesions (Shaw et al., 2004). To investigate this possibility, Amaral and colleagues carried out a series of studies in which the amygdala was lesioned bilaterally in rhesus monkeys at 2 weeks of age and social interactions were assessed at 6, 9 and 12 months of age (Bauman et al., 2004a; Bauman et al., 2004b; Prather et al., 2001). The results show a host of complex and subtle behavioural changes, which will be summarised below.

In response to novel, non-social objects, the effect of amygdala lesion in infant monkeys mimicked that found in adult animals: namely, a failure to apply species-typical caution to the situation. However, during social encounters the findings were strikingly different. Neonatally lesioned monkeys produced more fear behaviours (fear grimaces, screams etc) in a social situation compared to both hippocampus and sham lesioned controls (Bauman et al., 2004b; Prather et al., 2001). This is in contrast to monkeys lesioned in adulthood, who become socially unfearful (Emery et al., 2001). Despite this, infant-lesioned monkeys do engage in affiliative social behaviour, even to a significantly greater degree.
than control animals in the case of certain behaviours, such as following, cooing and grunting (Bauman et al., 2004b). However, the amygdala-lesioned subjects did engage in less physical contact than controls (Bauman et al., 2004b). Interestingly, the control lesioned animals spent more time in proximity to other controls, whereas the amygdala-lesioned subjects spent more time with other lesioned animals (Bauman et al., 2004b). This raises the possibility that the amygdala lesioned animals were unable to integrate fully with the control animals, perhaps due to a failure to perceive or comprehend subtle social cues. After each social interaction, trained observers, blind to lesion status, rated each monkey on a macaque ‘personality’ scale (Capitanio, 1999). Amygdala-lesioned animals were judged to be more nervous, more fearful, less confident and less active than controls (Bauman et al., 2004b).

In experiments designed to test the development of mother-infant interactions in the amygdala-lesioned monkeys, Bauman et al. (2004a) found essentially normal interactions, with the exception of increased physical contact time between infant and mother. In a ‘mother preference’ test that allowed the infants to choose between their mother and another familiar female, the amygdala-lesioned subjects did not preferentially seek proximity to their mother, unlike controls. However, they also produced fewer fear related behaviours during the task, leading the authors to conclude that, rather than lacking attachment to their mothers, the amygdala-lesioned subjects failed to perceive the potential danger of the separation and so did not attempt to seek solace in their mothers company.

Taking these findings as a whole, Amaral (Amaral et al., 2003a; Amaral, 2003; Amaral et al., 2003c) has argued forcibly that amygdala-lesioned monkeys are capable of fundamental social behaviour and, therefore, that the amygdala is not an essential
component of the social-cognitive network. Instead, he suggests that the amygdala normally serves to detect potential threat in the environment and to mediate a behaviourally appropriate response. Amygdala lesion in adulthood removes this danger-detector, resulting in inhibition where cautious exploration would be the appropriate response. Neonatal lesions, however, produce increased fear responses in situations that would not normally elicit such a reaction. The reason for this divergence between the infant and adult lesioned animals is unclear, but Amaral and colleagues (Amaral, 2003; Amaral et al., 2003c; Bauman et al., 2004b) argue that, since the lesioned infants are able to engage in affiliative social behaviours, the developmental effect of the lesion is to disrupt fear-processing rather than to fundamentally impair social cognitive ability. However, as Baumann et al. (2004b) concede, they were not able to directly evaluate how the amygdala-lesioned subjects interpreted or responded to specific social cues. Given the unusual findings of inappropriate fear responses combined with increases in certain affiliative behaviours, along with the fact that amygdala-lesioned animals may not have become fully integrated with controls, it is possible that the neonatal amygdala lesions led to subtle impairments in the ability to perceive and interpret social signals. More work is needed to examine this possibility before any firm conclusions can be made regarding the precise role of the amygdala in the development of primate social cognition. For example, we know that when viewing a face, monkeys normally fixate the eye region more than the other facial features (Keating and Keating, 1982; Nahm et al., 1997). Given the eyetracking results with SM, it would be interesting to compare the visual fixation patterns of rhesus monkeys to faces before and after neurotoxic lesion of the amygdala. Following ibotenic acid amygdala lesions in rats, Van Ree and colleagues report similar changes to social behaviour as those observed in primates, demonstrating the evolutionary history of the amygdala's role (Daenen et al., 2002; Diergaarde et al., 2004; Diergaarde et al., 2005; Wolterink et al., 2001). Furthermore, as with rhesus
monkeys, results differ depending on whether the lesion was produced neonatally or when the animal is mature. The full spectrum of results is complex but the basic finding is that amygdala lesion reduces social behaviour and that this reduction is greater in animals lesioned on day 7 of life than those lesioned on day 21 of life. The authors have not tested the responsiveness of the rats to novel, non-social objects but other work suggests that lesions of the lateral/basolateral nuclei of the rat amygdala disrupts normal fear responses to novel stimuli (Vazdarjanova et al., 2001). Therefore, the extent to which the social deficits following lesion are secondary to a more general disruption of threat processing remains unresolved. Another caveat of this work is that the rats were reared in isolation, possibly confounding any lesion effects. Despite these shortcomings, the work of Van Ree and colleagues is a useful cross-species replication of the general findings in primates.

The amygdala and fear recognition in humans

Several case reports have linked bilateral amygdala damage with an impaired ability to recognise facial expressions of emotions, especially in the case of fearful faces (Adolphs et al., 1994; Broks et al., 1998; Calder et al., 1996; Young et al., 1995; Young et al., 1996). Unilateral amygdala damage, however, does not appear to be sufficient to cause these deficits (Adolphs et al., 1995). Only one of the bilaterally lesioned patients, SM, has damage restricted to the amygdala (resulting from Urbach-Wiethe disease, Adolphs et al., 1994). The others suffered lesions following either encephalitis or surgery and, consequently, have sustained damage beyond the amygdala, in some cases substantially so. Despite this, basic visual perception appears normal in all of the reported cases, as tested by performance IQ or the Benton face matching test (Broks et al., 1998; Young et al., 1995). The idea that it is damage specifically to the amygdala, rather than to other
parts of the temporal lobe, that is the root cause of the emotion-recognition deficit is supported, on the one hand, by the existence of SM and on the other by the absence of a deficit in individuals with temporal lobe damage sparing the amygdala (e.g. Broks et al., 1998). In the most definitive study of this type, Adolphs et al. (1999) pooled data from several research groups to compare nine individuals with bilateral amygdala damage with both brain damaged and normal controls. This allowed sufficient power for group-wise statistical analysis and confirmed the major findings of the case reports: the amygdala damaged group were impaired at recognising all negative facial expressions but most severely for fear. It should be noted however, that individual performances in fear recognition ranged from extremely impaired to essentially normal, consistent with a case-report by Hamann et al. (1996), which found no fear recognition deficit in a patient with bilateral amygdala damage. Adolphs et al. (1999) suggest that such variability in impairment can be put down to the possibility of using compensatory cognitive strategies when attempting to recognise the emotional faces, but this has not yet been tested empirically.

Regarding the mechanism by which amygdala damage might lead to emotion recognition impairments, earlier reports suggest that, without a functioning amygdala, subjects have difficulty triggering a retrieval of knowledge concerning the emotion when presented with certain facial expressions (Adolphs et al., 1999). However, the work using the Bubbles task and eyetracking technology with SM (Adolphs et al., 2005, discussed above) points to a subtly different interpretation. SM’s poor fear recognition is apparently due to a failure of her amygdala to direct her visual system to fixate, pay attention to and make use of information from the eye region of faces. The fact that her fear recognition improves when she is directed to the eye region shows that she is, in fact, able to trigger the required emotional knowledge when she receives the necessary perceptual input. Her
problem lies in an inability to search automatically for this input, i.e. environmental clues of social or emotional relevance. This account may explain SM's impairments on other social tasks, such as judging trustworthiness of faces (Adolphs et al., 1998, see below). However, before any firm conclusions can be made, it would be useful to see SM's results replicated with other amygdala-damaged patients and, as discussed in the previous section, with non-human primates who have undergone amygdala lesion.

Neuroimaging studies with normal subjects have complemented the neuropsychological data. The amygdala is consistently activated when participants view fearful, compared to other (e.g. neutral or happy), faces (Morris et al., 1996; Morris et al., 1998a; Morris et al., 1999; Phillips et al., 1998; Thomas et al., 2001; Whalen et al., 1998; Winston et al., 2003a). The evidence regarding the other emotions is less clear, although both sad (Blair et al., 1999) and angry (Adams et al., 2003) faces have been shown to activate the amygdala under certain circumstances. Winston et al. (2003a) report compelling data, showing that the amygdala responds to high versus low intensities of all emotional expressions, including happy faces. They conclude that, rather than being fear or even negative-emotion specific, the amygdala responds to any stimulus of high emotional significance. This accords with recent data using olfactory (Anderson et al., 2003) or gustatory (Small et al., 2003) stimuli, showing amygdala activation varies with stimulus arousal, but not valence. That activation is more consistent to negative compared to positive expressions may reflect the fact that, in primate evolution, negatively-valenced stimuli have become more arousing than positive ones (Anderson et al., 2003; Ito et al., 1998). That activation to fearful faces is especially reliable may be because these are inherently the most arousing images and/or because, presented as they almost invariably are with forward looking gaze, the fearful faces are ambiguous – a feature which is capable in itself of causing amygdala activation (Adams et al., 2003; Whalen, 1999).
The amygdala and other areas of human social cognition

Given the evidence from primates and rats that the amygdala is important for social behaviour, a number of researchers have attempted to extend the link between the amygdala and emotion recognition in humans to wider areas of human social cognition, such as the ability to 'mentalise'. An early example is the finding that patients with bilateral amygdala damage judge faces to be more approachable and trustworthy than do controls (Adolphs et al., 1998). Evidence corroborating this finding comes from a fMRI study with healthy individuals: the amygdala is automatically engaged when viewing faces rated by the observer as untrustworthy, even if the subject is occupied in an incidental task, such as assessment of age (Winston et al., 2002).

However, interesting though this finding is, it could easily be explained by the theory of the amygdala as an automatic and presumably often unconscious 'danger-detector'—it does not necessarily follow that the amygdala is required for a higher-order understanding of the thoughts and feelings of others, as some have suggested it is (e.g. Baron-Cohen et al., 2000a). Attempts to implicate the amygdala in such 'on-line' mentalising have met with limited success. The one neuropsychological paper to find a positive result is that of Stone et al. (2003), who report that two patients with bilateral amygdala damage have difficulties with two theory of mind tasks: one testing the ability to recognise faux pas in verbal stories and the other testing the ability to recognise mental states from the eye region of faces. The amygdala lesioned subjects show clear impairments on both tasks; however there are a number of caveats to bear in mind with

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4 As Amaral (2003) points out, the behaviour of the amygdala-damaged subjects described by Adolphs et al. (1998) is highly reminiscent of the social uninhibition seen in adult monkeys following amygdala lesion (Emery et al., 2001).
these data. Firstly, damage is extended beyond the amygdala in both cases, including extensive damage to the right temporal lobe in one subject and areas of the basal ganglia and external capsule in the other. Secondly, the controls were not matched with the lesioned subjects in terms of IQ\(^5\). Given the verbal nature of both tasks and the fact that the verbal IQs of the amygdala lesioned patients in Stone et al.'s (1999) paper are relatively low (82 and 99) it would have been pertinent to have at least measured the IQ of the control subjects. Finally, given the fact that amygdala damage may impair the ability to make adequate use of information from the eyes (as seen with SM), the "reading the mind in the eyes" task is an inappropriate test of 'pure' mentalising ability in this subject group.

Evidence of an 'on-line' role of the amygdala in mentalising tasks is equally limited in the neuroimaging literature. As Gallagher and Frith (2003) point out in their review, among all the neuroimaging studies of theory of mind only Baron-Cohen et al. (1999b) have found amygdala activation. In this study, participants viewed pictures of eyes depicting an emotional expression: amygdala activation was present when subjects judged the emotion, but not the gender, of the stimuli. Given the well established role of the amygdala in emotion processing, it is feasible that this activation reflects the emotional content of the pictures rather than the process of mentalising per se.

As we have seen, the evidence of a role for the amygdala in 'on-line' mentalising is far from conclusive. However, given its well established function as a detector of socially salient stimuli (Sander et al., 2003), it has been suggested that the amygdala might be

\(^5\) The authors claim that earlier work shows that the faux pas test does not correlate with IQ (Baron-Cohen et al., 1999a). However, examination of this data shows that, although not significant, there is a trend towards a positive correlation between performance on the task and verbal IQ \((r=0.3, p=0.1)\).
important for the *development* of ToM abilities (Gallagher and Frith, 2003; Grelotti et al., 2002, see subsequent section for an exposition of this argument). Neuropsychological evidence for this is more promising. For example, Fine et al. (2001) report a patient with early left amygdala damage and a diagnosis of AS and schizophrenia who was impaired on second-order false belief tasks, comprehension of mental state cartoons and advanced ToM stories requiring participants to understand non-literal utterances such as white lies or sarcasm. Of course, such results would be expected from someone with a diagnosis of AS and so these data should be interpreted with caution: it is impossible to say whether the early amygdala lesion had a causal role in the incidence of AS or whether the occurrence of both in the same person is coincidental. More promising data comes from Heberlein et al. (2004) who studied a patient whose amygdala lesion is thought to have occurred in childhood or adolescence. The patient was asked to describe what was happening in the Heider and Simmel (1944) cartoons of geometric shapes. Whereas normal subjects interpreted the shapes as being social agents pursuing goals and having feelings, the patient failed to do so, describing the movements in purely mechanistic terms. In this regard, the amygdala damaged patient was similar to patients with an autistic-spectrum disorder (Abell et al., 2000). However, the best evidence that early amygdala damage can impair later ToM performance comes from Shaw et al. (2004). These authors compared ToM performance between a group of subjects who suffered congenital or childhood amygdala lesion with a group whose lesions arose in adulthood. The early damage group were impaired on the more advanced ToM tasks, such as detecting tactless comments or interpreting non-literal utterances, compared to both the healthy control group and the late amygdala damage group. Furthermore, these results held even after controlling for measures of executive function, memory and general intellectual ability.
Theories of the neurodevelopmental role of the amygdala in social cognition

Considering the evidence above as a whole, including both the human and animal research, there is not strong evidence that the amygdala is essential for ‘on-line’ social interaction. Instead, the role of the amygdala seems largely restricted to detecting and then enhancing the perception for, and memory of, socially and emotionally salient events (Dolan, 2002). In adults, impairment of this neuromodulatory system appears to result in two main social problems: firstly, a failure to approach a social situation with the appropriate caution, resulting in an over-trusting and socially uninhibited manner, and, secondly, failing to be drawn to the most emotionally meaningful aspects of the environment (such as eyes), resulting, for example, in occasional errors in reading someone’s emotional state. ‘Fundamental’ social interaction is generally unaffected. As Amaral (2003) suggests, this is perhaps because individuals (be they humans or primates) have had a life time to acquire and store social knowledge before their amygdala was damaged. They can therefore call upon past experience to understand social situations and to react appropriately – mediated perhaps by undamaged areas of the social brain, such as the prefrontal cortex.

However, as discussed in the previous section, it has been suggested that damage to the amygdala early in development could impair the ability to accrue social knowledge, thereby resulting in more profound social-cognitive deficits later in life. Several theorists have argued that social-cognitive abilities, such as theory of mind, build upon basic social-perceptual knowledge and have implicated the amygdala in this (Baron-Cohen, 1994; Hobson, 1993; Tager-Flusberg and Sullivan, 2000) but Schultz and colleagues (Grelotti et al., 2002; Schultz et al., 2000b; Schultz, 2005) have provided the most
complete theory of how this might occur. According to this model, the amygdala flags social stimuli, such as faces and eyes, as salient and then, via feedback connections, influences the cortical sites where the actual computations of these stimuli are performed (e.g. the STS and FFA) to process the stimuli more deeply and for longer. Over time, this facilitates social-perceptual learning. In the next stage of the model, skill in perceiving social stimuli to obtain information such as person identity or emotional state is hypothesised to be of critical importance for the development of social skills. Social-perception ability provides the ‘scaffolding’ necessary during social interactions to understand the barrage of non-verbal communications that occur in rapid succession.

To date, evidence for the model is restricted to what we know about the amygdala’s role in healthy adults and to the work showing that amygdala lesions acquired early in life can have more profound effects on later social-cognitive function than lesions acquired in adulthood. More direct, neurodevelopmental, evidence is certainly required. However, the model does have some plausibility and it can be brought to bear to help explain the possible role of the amygdala in autistic spectrum disorders, which is the topic of the next section.

Evidence implicating the amygdala in autistic-spectrum disorders

Cellular pathology of the amygdala in ASDs

Bauman and Kemper (1985) examined the microscopic organisation of six post-mortem autistic brains. Nissl stained sections of brain tissue from autistic cases were compared to
age-matched controls in which corresponding areas were compared under the microscope. They report that neurons in the amygdala of the autistic subjects were unusually small and more densely packed than those of controls. In a later review, Kemper and Baumann (1993) suggest that this pathology is indicative of a curtailed neuronal maturation. The only other study to examine the cellular pathology of the amygdala in autism also examined six post-mortem autistic brains (Bailey et al., 1998). However, in this case the authors were unable to find any significant differences compared to control brains.

Both of these studies suffer from two major drawbacks. Firstly, they are both complicated by including a number of cases who, as well as having autism, suffered from epileptic seizures. Epilepsy itself is associated with cell loss in the amygdala (Pitkanen et al., 1998) and may be a confounding factor in the autism studies. Secondly, both studies did not conduct quantitative analysis. Therefore, although suggestive and theoretically interesting, the results of Bauman and Kemper (1985) require urgent replication.

**Structural MRI studies**

There have been at least 15 MRI studies investigating the structure of the amygdala in autistic-spectrum disorders; these are summarised in table 1. Findings have been remarkably inconsistent, with results showing increases (Abell et al., 1999; Howard et al., 2000; Schumann et al., 2004; Sparks et al., 2002), decreases (Aylward et al., 1999; Herbert et al., 2003; Nacewicz et al., 2006; Pierce et al., 2001; Rojas et al., 2004; Yamasue et al., 2005) and no differences (Bigler et al., 2003; Dziobek et al., 2006; Haznedar et al., 2000; Palmen et al., 2006) in amygdala volume between autistic groups and controls. There is substantial variation amongst these studies in terms of the method of volumetry employed, the types of potentially confounding factors controlled for and, not least, in
terms of the characteristics of the subject groups (see table 1). Of the latter, the age of the participants has proven to be a crucial factor and when this is taken into account, a comprehensible pattern begins to emerge from the data. For example, Schumman et al. (2004) show that, in normally developing children, there is a steep linear increase in amygdala volume from infancy to late adolescence. In autistic children, however, this trend is not apparent; instead the amygdala is already of a large size in infancy but seemingly remains this size throughout development. The result is that autistic children will tend to have bigger amygdala than controls if tested in early childhood but show no differences in adolescence. This broad pattern (the absence of normal amygdala growth through development) has been replicated by Nacewicz et al., (in press). However, they show that in adolescence and progressing into adulthood, the amygdala of autistic individuals may be reduced in volume compared to controls. Overall, this pattern of an increased amygdala volume in early childhood, no difference in adolescence and a decreased volume in adulthood is largely supported by the literature. For example, Sparks et al. (2002) found greater amygdala volumes in a group of 2-5 year olds with autism. Bigler et al. (2003) and Palmen et al. (2006) find no differences between groups with a mean age in the middle of adolescence (14 and 15 years respectively). Finally, with adults samples (mean age > 20 years), Aylward et al. (1999), Pierce et al. (2001) and Rojas et al. (2004) all found smaller amygdala volumes relative to controls.
<table>
<thead>
<tr>
<th>Name &amp; Year</th>
<th>Technique</th>
<th>Number of Subjects and Diagnosis</th>
<th>Age Mean(SD) Range</th>
<th>Controlled for?</th>
<th>Amygdala volume findings</th>
<th>Other findings</th>
<th>Control for brain volume?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aylward et al. 1999</td>
<td>Manual tracing</td>
<td>14 HFA (IQ&gt;80) Clinical diagnosis, confirmed with ADI-R and ADOS</td>
<td>20.5 yrs (1.8) 11 - 37 yrs</td>
<td>Age, sex, IQ, family socioeconomic status</td>
<td>↓ AMY</td>
<td>↓ hippocampus</td>
<td>Yes.</td>
</tr>
<tr>
<td>Abell et al. 1999</td>
<td>VBM</td>
<td>15 HFA Clinical diagnosis, confirmed with an unspecified checklist. The rater does not appear to have been blind to subject group.</td>
<td>28.8 yrs (6.6)</td>
<td>Age, sex, handedness, IQ</td>
<td>↑ AMY</td>
<td>↓ right paracingulate, ↓ left inferior frontal gyrus, ↓ left occipito-temporal junction, ↑ anterior lobe of cerebellar hemisphere, ↑ pyramid of cerebellar vermis, ↑ left middle temporal gyrus, ↑ right inferior temporal gyrus</td>
<td>No</td>
</tr>
<tr>
<td>Pierce et al. 2001</td>
<td>Manual tracing</td>
<td>7 Autism Clinical diagnosis, confirmed with ADI-R, ADOS and Childhood autism rating scale</td>
<td>29.5 yrs (8.0) 21 - 41 yrs</td>
<td>Sex, age, handedness</td>
<td>↓ AMY</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Haznedar et al. 2000</td>
<td>Manual tracing</td>
<td>10 Autism 7 AS Clinical diagnosis, Confirmed by ADI-R in 13 individuals</td>
<td>27.7 yrs (11.3)</td>
<td>Sex, age</td>
<td>No differences between control group and either the autistic or the AS group</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Howard et al. 2000</td>
<td>Manual - point counting</td>
<td>10 mixed autism and AS (numbers not specified) Clinical diagnosis, NOT confirmed</td>
<td>15.8 - 40 yrs</td>
<td>Sex, age, verbal IQ</td>
<td>↑ AMY</td>
<td>Trend towards ↓ hippocampus</td>
<td>No</td>
</tr>
<tr>
<td>Sparks et al. 2002</td>
<td>Manual tracing</td>
<td>29 Autism 16 PD-NOS Clinical diagnosis, confirmed with ADI-R and ADOS</td>
<td>4.0 yrs (0.4) 2.2 - 4.7 yrs</td>
<td>Age, sex</td>
<td>Autism: ↑ AMY PD-NOS: No difference after controlling for total brain volume</td>
<td>None after correcting for total brain volume</td>
<td>Yes</td>
</tr>
<tr>
<td>Salmond et al. 2003</td>
<td>'Individual' VBM</td>
<td>3 HFA 11 AS Clinical diagnosis, NOT confirmed</td>
<td>12.9yrs (8 -18 yrs</td>
<td>Age only. NOTE: Sex ratios poorly matched</td>
<td>7/14 show abnormal grey matter density in the amygdala</td>
<td>7/14 show hippocampal abnormalities, 13/14 show OFC abnormalities, 10/14 show STG abnormalities, 11/14 show cerebellum abnormalities, 0/14 show visual cortex abnormalities (control)</td>
<td>No</td>
</tr>
<tr>
<td>Herbert et al. (2003)</td>
<td>Semi-automated segmentation into principal grey matter structures</td>
<td>17 HFS (IQ&gt;80) Wing Autistic Disorder Interview Checklist, confirmed by blind clinical diagnosis</td>
<td>7 - 11 yrs</td>
<td>Sex, age</td>
<td>↓ Amygdala-hippocampal complex</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Sigler et al. 2003</td>
<td>Manual tracing</td>
<td>26 normocephalic autism NC:</td>
<td></td>
<td>Age, sex</td>
<td>No differences</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Methodology</td>
<td>Number</td>
<td>Diagnosis</td>
<td>Age</td>
<td>Sex</td>
<td>Amygdala</td>
<td>Hippocampus</td>
</tr>
<tr>
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</tr>
<tr>
<td>Schuman et al. 2004</td>
<td>Manual tracing</td>
<td>19 LFA (IQ&lt;70)  27 HFA (IQ&gt;70)  25 AS (IQ&gt;70 plus no language delay)</td>
<td>Clinical diagnosis, confirmed with ADI-R and ADOS</td>
<td>7.5 - 18.5 yrs</td>
<td>Age and sex</td>
<td>7.5 - 12.5 yr olds</td>
<td>Hippocampus enlarged at all ages (significant for LFA and HFA, only a trend for AS)</td>
</tr>
<tr>
<td>Rojas et al. 2004</td>
<td>Manual tracing</td>
<td>15 Autism</td>
<td>Clinical diagnosis, confirmed with ADI-R and ADOS</td>
<td>30.3 yrs (9.1)</td>
<td>Sex</td>
<td>↓ AMY</td>
<td>↓ Hippocampus</td>
</tr>
<tr>
<td>Dziobek et al. 2006</td>
<td>Manual tracing</td>
<td>17 AS</td>
<td>Clinical diagnosis, confirmed with ADI-R</td>
<td>41.4 yrs (9.9)</td>
<td>Age, sex, education, IQ</td>
<td>No diff before or after controlling for brain volume.</td>
<td></td>
</tr>
<tr>
<td>Palmen et al. 2006</td>
<td>Manual tracing</td>
<td>21 HFA  21 AS</td>
<td>Clinical diagnosis, confirmed with ADI-R</td>
<td>15.6 yrs (5.25) 7 - 25 yrs</td>
<td>Age, sex, IQ, parental education, handedness, height, weight</td>
<td>No differences</td>
<td>No correlation between social scale of ADI-R and amygdala or hippocampal volume</td>
</tr>
<tr>
<td>Nacewicz et al. in press</td>
<td>Manual tracing</td>
<td>23 Autism  5 AS</td>
<td>Clinical diagnosis, confirmed with ADI-R</td>
<td>15.4 yrs (4.6) 8 - 25 yrs</td>
<td>Age, sex, IQ</td>
<td>8 - 12.5 yr olds</td>
<td>+ve correlation between AMY volume and number of fixations on the eye region of faces</td>
</tr>
</tbody>
</table>
Of the studies that do not fit with this age-related pattern, both Abell et al. (1999) and Howard et al. (2000) found increases in amygdala volume in groups of adults with an ASD. However, neither of these studies controlled for differences in total brain volume - a major deficiency given that there is much evidence of general cerebral enlargement in ASD (e.g. Courchesne and Pierce, 2005a). Herbert et al. (2003) report reductions in the volume of the amygdala-hippocampal complex (reported as a single entity) in young children. However, this is difficult to interpret, as changes in the amygdala and the hippocampus do not always co-vary (e.g. Howard et al., 2000; Salmond et al., 2003; Schumann et al., 2004). This leaves two studies (Haznedar et al. 2000; Dziobek et al., 2006), which do not fit into the pattern described above, both of which found no differences between adult samples of cases and controls (where a reduction in amygdala volume would have been expected). The subject groups of these latter studies contained only (Dziobek et al., 2006), or a substantial proportion of (Haznedar et al., 2000), high-functioning (AS) individuals, whereas earlier studies typically contained a number of more severely autistic subjects. Recent work appears to suggest that severity of autistic symptoms may interact with age to predict volume changes in the amygdala, as will be discussed below.

On the basis of their data, Nacewicz et al. (in press) suggest that both age and severity of autistic symptoms influence amygdala volume in ASD. As well as the age-related differences discussed above, the authors report that amygdala volume in ASD was negatively correlated with both the non-verbal communication and the social reciprocity scale of the ADI-R: that is, the autistic subjects with the smallest amygdala showed the most impairment. Interestingly, these findings are echoed in the results of an eye-tracking experiment of emotion recognition on the same individuals (Nacewicz et al., in press). Autistic subjects with the smallest amygdala showed the slowest judgement of emotional
expressions and the least fixation on the eye regions of the faces. Therefore, smaller amygdala volume was associated with increased severity of social impairment, measured by both a standard diagnostic interview and by behavioural data of eye fixations.

In light of the above, the negative findings of Haznedar et al. (2000) and Dziobek et al. (2006) are perhaps not as inconsistent with the pattern emerging from the other structural MRI studies as would first appear. Although they find no significant differences with healthy controls, Haznedar et al. (2000) do find that the amygdala of their AS subjects is significantly larger than that of the autistic patients. Furthermore, across the combined Asperger and autism groups, left amygdala volume is negatively correlated with impairments in non-verbal communication as measured by the ADI-R. Dziobek et al. (2006) show a non-significant trend towards similar negative correlations between all sub-scales of the ADI-R and amygdala volume. Therefore, there is an emerging consensus of a link between measures of social impairment and structural pathology of the amygdala in ASD. Impairment appears to interact with age to predict amygdala volume: enlarged amygdala in childhood make way to either normal or abnormally small amygdala volumes in adulthood, depending on the severity of autistic symptomology.\(^6\)

These data beg two related questions: firstly, what is causing the dynamic changes in amygdala volume over time in ASD and, secondly, what does it mean, on a cellular level, for an amygdala to be abnormally large or small? To answer this first question, Nacewicz et al. (\textit{in press}) propose a model of hyper-activity induced enlargement followed by atrophy. Analogous to stress-induced dendritic cell arborisation observed in the amygdala

\[\text{\textit{in press}}\]

\(^6\) One very important caveat regarding this conclusion is that, so far, all the studies have been cross-sectional. Longitudinal studies are required to unequivocally demonstrate dynamic changes in amygdala volume through development.
of rats, the supposedly hyperactive amygdala of an individual with ASD at first becomes enlarged before undergoing excitotoxic cell loss and consequent atrophy. This 'hyperactive' amygdala model – linked to the idea that those with an ASD are hyper-aroused by social stimuli - is one of the two major theories currently being considered as an explanation of the amygdala’s involvement in ASD. It is discussed in more detail in a subsequent section. As for the second question of how volume changes relate to cellular pathology – one can only speculate given the current knowledge and techniques. As discussed above, Nacewicz et al. (in press) turn to animal models of chronic stress for suggestions but it is clear that more work is required using post-mortem preparations of tissues from autistic brains.

**fMRI studies**

Perhaps surprisingly, given the structural findings, evidence for functional abnormalities of the amygdala in ASD is thin on the ground. What little evidence there is usually employs visual stimuli depicting emotional expressions. For example, Baron-Cohen et al. (1999b) have shown that the amygdala is activated when normal subjects judge what a person is thinking or feeling from looking at their eyes. Individuals with ASD, however, do not show this activation. Others have reported that amygdala activity in high-functioning individuals with autism is blunted compared with controls when implicitly processing emotional expressions (Critchley et al., 2000). Using a similar task, Welchew et al. (2005) show evidence of a functional connectivity between the amygdala and parahippocampal gyrus in controls but not in those with an ASD.

However, a major problem with these studies is that they did not measure the fixation patterns of subjects during the experimental tasks. There is substantial evidence
(discussed in the next section) that individuals with an ASD do not explore faces normally – in particular they spend less time fixating the eyes (e.g. Klin et al., 2002; Pelphrey et al., 2002). Therefore, it is unclear whether the lack of amygdala activation in response to faces is a result of abnormal neural functioning or simply a failure to engage with the salient aspects of the stimuli. Recent evidence by Dalton et al. (2005) suggests it might be the latter: in a concurrent eye-tracking and fMRI study where faces were presented, the autistic subjects spent less time fixating the eye region, as expected. However, amygdala activation correlated with the time spent fixating the eyes in the autistic group, which may indicate that the autistic amygdala can respond normally given the necessary visual input (however, as discussed later, this needs to be confirmed in studies where gaze fixation is manipulated within the same individual).

Inferences from neuropsychology

Some of the most provocative, albeit somewhat circumstantial, evidence for involvement of the amygdala in ASD comes from neuropsychology: autistic individuals show a variety of impairments that are reminiscent of patients with bilateral amygdala damage. For example, there have been reports that individuals with autism are impaired at recognising fear, and to a lesser extent sadness, anger and disgust, in facial expressions of emotion (Howard et al., 2000; Pelphrey et al., 2002). However, there have also been a number of negative findings (Adolphs et al., 2001; Castelli, 2005; Grossman et al., 2000). The latter two of these studies were conducted with children (mean chronological age 11.8 and 12.3 respectively, verbal age 9.3 years for the second study) rather than adults, which may go some way to explaining the negative findings. For example, control children may not yet be developed enough to complete the task successfully, which
would appear to be the case in the Grossman et al. (2000) study where control children only correctly identified 50% of the fearful faces (AS children identified 48% correctly).

The other negative finding, by Adolphs et al. (2001), warrants further consideration. In this study, facial emotion recognition performance is compared between a group of 7 high-functioning autistic adults, 8 subjects with bilateral amygdala damage and 18 normal controls. Despite not presenting statistics to specifically compare each group pair (presumably because of the small sample sizes), the authors claim that the 'autistic subjects gave normal ratings to facial expressions [of the emotions]' (Adolphs et al.; 2001, page 234). However, for fearful faces, 6 out of 7 autistic subjects gave responses below the mean for normal controls and this deficit was by at least 1 standard deviation in 4 of the 6 cases (Adolphs et al., 2001, figure 2). A similar, albeit less severe, pattern is seen for sad and disgusted expressions. It is true that, in general, the autistic performance was better than that of the amygdala damaged participants (although, again no statistical test of this is presented). However, as the authors point out, some individual autistic performances are as poor as the worst results of the amygdala damaged group, indicating the possibility that a subset of autistic individuals may be disproportionately impaired. Interestingly, both Howard et al. (2000) and Pelphrey et al. (2002) report much greater variance for autistic fear recognition responses than for control responses. This variability and the reasons for it deserve further investigation and form part of the rationale behind the experiments presented in chapters 4 and 5 of this thesis.

Although there is some debate about the existence of a 'basic emotion' recognition deficit in ASD, the finding that such individuals have problems inferring complex 'social' emotions from faces (and particularly the eye region) has not been contested (Baron-Cohen et al., 1997a; Baron-Cohen et al., 1997b; Baron-Cohen et al., 2001a). As discussed
in an earlier section, patients with amygdala damage have been shown to be impaired at the same task used by Baron-Cohen and colleagues (Adolphs et al., 2002). In fact, like autistics, amygdala lesioned patients are typically worse at recognising the 'social' emotions than the 'basic' ones.

As well as the test of basic emotion recognition, Adolphs et al. (2001) compared high-functioning autistic adults to bilateral amygdala damaged subjects and healthy controls on a test of 'social judgement from faces': subjects had to judge the trustworthiness of a series of individuals from facial photographs. Like amygdala damaged patients, autistic individuals gave abnormally positive ratings to those faces which controls rate as the most negative.

Finally, there is consistent evidence that, like SM, autistic individuals scan faces abnormally, spending less time fixating on the eye region than normal controls (Dalton et al., 2005; Klin et al., 2002; Pelphrey et al., 2002; Nacewicz et al. in press). Interestingly, the one study to not produce this result was conducted with children (van der Geest et al., 2002), which perhaps goes someway to explaining the failure to find a fear recognition deficit in younger individuals with ASD (Castelli, 2005). Given the evidence that structural amygdala volumes may develop from abnormally large in childhood to abnormally small in adulthood and the fact that smaller amygdala volume is associated with less eye fixation and poorer fear recognition, it is an intriguing possibility that the development of these three variables (amygdala volume, eye fixation and fear recognition) is linked. A longitudinal study could provide useful insight into this issue.
The relevance of the non-human primate amygdala lesion data

As discussed in a previous section, Amaral has argued forcibly that the amygdala is not required for the expression of species-typical social behaviour in the adult or for its development in infants (Amaral, 2003; Amaral et al., 2003c). This is based largely on the fact that amygdala lesioned monkeys can and do engage in affiliative social behaviour, such as cooing, grunting and grooming (Bauman et al., 2004b; Emery et al., 2001; Prather et al., 2001). Based on these findings, Amaral and colleagues go on to argue that amygdala pathology must therefore not be involved in producing abnormal social behaviour in autism (Amaral et al., 2003a; Amaral and Corbett, 2002). Instead, if it is involved at all, it may be with producing the anxiety which is commonly experienced by autistic individuals (parallels are drawn here to the increased social fear exhibited by neonatally lesioned monkeys; Baumann et al., 2004b). However, these conclusions may be a little premature. It is true that the lesioned monkeys do not become socially withdrawn but it is not yet clear whether their perception and interpretation of social signals is entirely normal. Neonatal lesions produced a complex and subtle set of behavioural changes later in life (Baumann et al. 2004b). At 12 months old, the lesioned monkeys exhibited both inappropriate social fear and increased affiliative behaviour. Coupled with this, there is some evidence that the lesioned animals were not fully integrated into the non-lesioned group. It is therefore possible that the lesioned monkeys were impaired in their ability to perceive and accurately interpret social cues from conspecifics. More work with these monkeys, using specifically designed behavioural tasks, is required to provide a definitive answer to this issue.
Overview

Overall, a link between the amygdala and ASD seems probable, but its nature remains uncertain. Taking subject age and the severity of autistic symptoms into account, the structural imaging data begins to provide a comprehensible picture and suggests hypotheses regarding dynamic abnormalities of amygdala structure, which can be tested with longitudinal studies. Of immediate concern, however, are the cellular correlates of these volumetric changes: existing post-mortem studies are flawed and require replication. The neuropsychological literature demonstrates some parallels between autistic individuals and patients with focal amygdala damage, consistent with the notion that amygdala dysfunction may contribute to autistic symptoms. However, identical symptoms can have diverse aetiologies and a causal role of the amygdala in the social-cognitive deficits of ASD is far from proven. Perhaps functional neuroimaging experiments can shed light on this matter, although, to date, studies have been flawed by confounding neural and behavioural abnormalities. What is needed is a theory (or theories) predicting a specific role for the amygdala, which can lead to clear, falsifiable hypotheses. Two candidate theories have come to the fore in recent years and will be discussed in the following section.

Neurodevelopmental theories of the amygdala's role in autistic-spectrum disorders

The two theories are based on the idea that failure to orient towards the socially meaningful parts of the environment can cause deficits in social perception and, if it occurs early in life, may deleteriously affect the development of social knowledge and understanding (see earlier section and Schultz, 2005; Tager-Flusberg and Sullivan, 2000). Both theories suppose that this kind of social inattention is present in ASD and that the
amygdala plays a part in this. However, they differ in what they believe are the root causes of the social inattention, as will be explained below.

Lack of 'social interest' – Amygdala hypo-activation

A number of groups have presented variations of this theory (e.g. Critchley et al., 2000; Baron-Cohen et al., 2000) but its most vocal supporters have been Schultz and colleagues (Grelotti et al., 2002; Schultz et al., 2000b; Schultz, 2005). The basic premise is that during development, either through impairment with associative learning or via a failure of brain inter-connectivity, the amygdala is unable to flag social stimuli as meaningful. Neurophysiologically this would present as an amygdala hypo-activation in response to social stimuli, manifesting behaviourally as a 'lack of social interest'. The result is reduced processing in cortical areas where high-level computations of social stimuli usually take place – e.g. the FG and STS. This reduced processing could occur both directly, through a lack of amygdala neuromodulation of the FG or STS via feedback connections, or more indirectly through reduced attention and orientation towards the stimuli. Either way, over time the net result is hypothesised to be a hindering of social-perceptual learning and consequent underdevelopment of social-perceptual skills. These abilities are thought to provide a building block for higher-order social-cognitive abilities, such as ToM, and to provide the 'scaffolding' necessary to understand the barrage of non-verbal communications that occur during social interaction (Baron-Cohen, 1994; Hobson, 1993; Schultz, 2005; Tager-Flusberg and Sullivan, 2000). Therefore, this sequence of events, beginning with a failure to orient towards socially meaningful stimuli early in life, could result in the development of profound social-cognitive impairment by adulthood.
Aversion to social stimuli – Amygdala hyper-activation

The hyper-active amygdala model suggests that affected individuals find social stimuli over-arousing and hence aversive. Therefore, such stimuli are actively avoided (rather than ignored, as proposed by the hypo-active amygdala model). Neurophysiologically, the model predicts heightened amygdala responsiveness to relevant stimuli (so long as attention is directed towards those stimuli), manifesting behaviourally as anxiety and autonomic arousal. Like the hypo-active model, the failure to orient towards socially meaningful parts of the environment causes problems with social-perception, which over time may develop into more profound social-cognitive difficulties. The hyper-active model has its roots in the work of Hutt and Ounsted (1969), who suggested that individuals with autism actively avoid eye-contact in order to reduce the over-arousal produced in them by these stimuli, but the major proponents of its modern incarnation are Richard Davidson, David Amaral and colleagues (Amaral and Corbett, 2002; Dalton et al., 2005; Nacewicz et al., in press).

Evidence, predictions and other considerations

To date, much of the available evidence could apply equally well to either the hyper-active or the hypo-active theory – the finding that autistics spend less time fixating the eye region of faces for example. However, some preliminary evidence for the hyper-responsive model has come to light. I will review this and then suggest a number of testable predictions based on both of the theories. The section then ends by discussing the idea that both theories could apply, but to different sub-sets of individuals with ASD, and by considering the place of the amygdala theories of autism within the broader suite of neurocognitive models of the disorder.
The finding that neonatal amygdala lesion in macaques affects social fear rather than 'fundamental social interaction' (Bauman et al., 2004a; Bauman et al., 2004b; Prather et al., 2001), has been cited in support of the hyper-activity model (for example, see Amaral and Corbett, 2002, pg. 17). However, how the removal of a structure relates specifically to hyper- rather than hypo-activity is unclear. Furthermore, as discussed earlier, it is still uncertain exactly how and if neonatal amygdala lesion affects subtle social cognitive processes. More research with neonatally lesioned monkeys is required but has the potential to shed much light on the role of the amygdala in autism.

In their concurrent fMRI and eyetracking study, Dalton et al. (2005) showed that eye fixation within autistics individuals (but not controls) was positively correlated with amygdala activation. This, the authors claim, suggests that autistics are hyper-aroused by looking at eyes and so avoid them. However, the data are also consistent with the hypo-functional model: perhaps the individuals looking at the eyes the least are doing so because their amygdala are under-active and so are not flagging the eyes as salient. The lack of a correlation amongst the controls could be due to a ceiling effect for eye-fixation – all the controls spent a significant time fixating the eyes. What is needed is an experiment where eye fixation is manipulated while amygdala activity or associated responses (such as SCRs) are measured. The hyper-active model would predict that autistics would show a greater response than controls when asked to look at the eyes, whereas the hypo-responsive model would predict the opposite effect. Self-report measures of arousal would also be beneficial – for example the hyper-activity model would predict that eye fixation amongst the autistics will be negatively correlated with measures of social anxiety, whereas the hypo-responsive model would suggest there would be no such correlation. Experiments testing some of these predictions are presented in chapter 5.
Nacewicz et al. (in press) found that autistic impairment interacts with age to predict abnormally large amygdala volume in childhood, followed by abnormally small amygdala volumes by adulthood. Furthermore, subjects with the smallest amygdala fixated the eye regions of faces the least. This, the authors conclude, is consistent with, 'a model of hyperactivity-induced changes' (initial outgrowth followed by atrophy) caused by heightened 'allostatic load' (Nacewicz et al. in press, pg. 20). As the authors readily admit, longitudinal studies are needed to substantiate the dynamic nature of their claims. However, the model also makes predictions which could be tested via cross-sectional studies. For example, if allostatic load is responsible for the volumetric changes (and for the lack of eye fixation) then autistic adults with the greatest levels of social anxiety should have the smallest amygdala – this prediction is tested in chapter 5.

As yet, no evidence specifically in support of the hypo-functional theory has been published. However, the model does proffer a number of testable predictions, some of which have already been discussed. Those not yet mentioned relate to the supposed failure of the amygdala in autism to flag a socially salient event and to modulate attention accordingly. This failure could occur in at least two ways: by an inability to form stimulus-salient associations or by a failure of amygdala-cortical modulation. The first of these could be examined in associative learning experiments, using, fear conditioning for example.\(^7\) One way the second could be investigated behaviourally is via experiments where attention is modulated by stimulus salience – an example paradigm is the emotional modulation of the attentional blink (Anderson and Phelps, 2001). Work of this kind is presented in chapter 6.

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\(^7\) I am aware of both positive (Goldsmith, personal communication) and negative (Schultz, personal communication) findings of a fear conditioning impairment in autism, but none of these studies have yet been subject to peer review.
One intriguing possibility is that both models apply, but to different sub-sets of individuals with an ASD. For example, while Hirstein et al. (2001) found elevated electrodermal activity in the majority of children with autism (70%), they also described a small sub-set (11%) with near absent responses. While this study is flawed by not making an objective measure of the focus of the children’s attention (by using eye-tracking for example), it does raise the possibility that there exists both autonomically hyper- and hypo-responsive sets of individuals. Perhaps parallels can be drawn here to behavioural classifications of autistic sub-types, which describe both ‘socially aloof’ and ‘active, but odd’ individuals (Wing and Gould, 1979). It will be theoretically important to verify the existence of the hyper- and hypo-responsive sub-types via studies involving large numbers of participants.

It is important to point out that the theories described above do not attempt to give an all-encompassing neurocognitive account of ASDs. Rather, they are theories of how the amygdala might be involved in the aetiology of some autistic symptoms. Many areas of the brain have been implicated in the pathophysiology of autism and evidence suggests that there might be diffuse abnormalities in brain development (for review see Brambilla et al., 2003), resulting in impaired inter-regional connectivity (Courchesne and Pierce, 2005a; Courchesne and Pierce, 2005b). The value of the amygdala theories is that they have the potential to explain the sometimes inconsistent body of evidence implicating the amygdala in ASDs. At best, however, they are likely to represent one of a number of ‘routes’ to social-cognitive impairment in this disorder.
Chapter summary, introduction to the experiments and predictions

It has been argued that social cognition represents a unique domain or module within the architecture of the mind, embodied in a distributed network of brain regions each somewhat specialised for the task of processing social information. In support of this, the existence of special populations, such as ASD and Williams Syndrome, as well as patients with focal brain damage, has shown that social- and non-social cognitive ability can vary independently. To date though, no studies have examined individual differences in social cognitive ability amongst the normal population and linked these to underlying neural function. In chapter 3 I attempt a first effort at such an experiment by investigating the variability in emotion recognition ability in the normal population. Specifically, because of its association with the amygdala and with disorders of social cognition such as ASD, I examine the ability to recognise fear from facial expressions. I predicted that:

a) poor ability to recognise fearful expressions would extend to social cognitive problems not directly related to face processing – namely, the Frith-Happe theory of mind task

b) in fMRI, poor ability to recognise fearful expressions would be associated with
   i. reduced activation of the amygdala and associated regions of the ‘social brain’ in response to socially salient stimuli
   ii. reduced functional integration between the amygdala and other areas of the ‘social brain’, such as the FG and STS

c) poor fear recognition ability would be associated with greater day to day difficulties with social interaction and communication
ASDs are disorders primarily of social cognition and a number of researchers have suggested that dysfunction of the amygdala may have a role to play in the pathology of the condition, citing neuroanatomical, neurophysiological and neuropsychological data (Baron-Cohen et al., 2000a;Sweeten et al., 2002). Of the latter, one controversial assertion is that, like patients with amygdala damage, individuals with an ASD are poor at recognising fearful expressions. In chapter 4, I investigate this claim and attempt to link it to another neuropsychological phenomenon of ASD which is reminiscent of patients with amygdala damage: the reduced amount of time spent fixating the eyes. Specifically, I predict:

a) an overall fear recognition deficit in a group of adults with an ASD
b) an overall reduced amount of time spent fixating the eyes in the ASD group
c) a link between fear recognition and time spent fixating the eyes, such that those with the lowest fear score are the subjects who fixate the eyes the least
d) that lower eye fixation and poorer fear recognition in the ASD group are associated with a greater degree of day to day social impairment

The exact nature of the amygdala's role within the social-cognitive network is a matter of considerable debate. With a few caveats, the weight of evidence suggests that the amygdala is not necessary for adequate social interaction in the adult. However, it may play a vital role in social-perceptual development, the disruption of which may lead to profound social-cognitive impairment later in life. This notion informs two recent theories of how the amygdala might be involved in ASD which differ in their proposed aetiology but converge in their later pathogenesis. In the hypo-functional model, the amygdala fails to flag social stimuli as significant, and so they are ignored. In the hyper-functional model, social stimuli cause amygdala-mediated over-arousal and so they are
avoided. In either case, the net result is an under-development of social-perceptual, followed by social-cognitive, ability.

In chapters 5 and 6 I present psychological, psychophysiological and neuroanatomical experiments with two, interrelated, aims:

1) to test predictions of the hyper- and hypo-active amygdala models of ASD in order to gain greater insight into the amygdala’s role in ASD and social cognition in general

2) to explain the root causes of the reduced eye fixation and poor fear recognition in ASD, along the lines proposed by the two competing models

Specifically, I examine:

a) the relationship, in ASD, between social anxiety and the amount of time spent fixating the eyes. The hyper-active model predicts that there will be a negative correlation between these two variables.

b) the relationship between the size of the autonomic response when made to look at eyes and the amount of time spent fixating eyes during free-viewing. The hyper-active model would predict a negative correlation between these two variables; the hypo-active model would predict a positive correlation.

c) the relationship between the volume of grey matter in the amygdala and:

i. the amount of time spent fixating the eyes

ii. fear recognition ability

iii. autonomic response to eyes

iv. level of social anxiety.
The hyper-active model would predict positive correlations between grey matter volume and (i) and (ii) above, but negative correlations with (iii) and (iv).

d) the ability of individuals with an ASD to show perceptual benefit for emotionally arousing stimuli, using an emotional modulation of the attentional blink paradigm. This ability has been shown to require a functioning amygdala and is thought to be a specific example of the amygdala's role in enhancing cortical processing in response to a salient event (Anderson and Phelps, 2001). The hypo-active model hypothesises that this system is disrupted in ASD and would therefore predict less perceptual benefit for arousing events in cases versus controls.
Chapter 2 – Methodology

Experimental groups

Low and normal fear scoring males

In chapter 3 I present a series of experiments on males from the normal population who showed either low (poor) or high (normal) ability to recognise fear in facial expressions. These individuals were picked from a large sample of UCL students and staff who took part in an on-line version of the Ekman-Friesen test of facial affect (see below). Exact details of this recruitment procedure and of the group characteristics are given in chapter 3.

AS group and their controls

In chapters 4 – 6 I present a number of experiments conducted with adults with an ASD. As this group was intended to function as a model for understanding normal social cognition, I decided to study only high-functioning (IQ > 90) individuals with a diagnosis of AS, rather than people with autism, which is often associated with lower functioning. It was felt that this group represented a sample with a more ‘pure’ social cognitive deficit, unadulterated by global cognitive impairment.

Recruitment

Subjects with AS were recruited from a number of sources. Adverts were placed in the National Autistic Society newsletter, on the ASPEN message board (part of the National Autistic Society website), in the Autism London newsletter and on a website that
provides information to university students with AS (http://www.users.dircon.co.uk/~cns/). In addition, a list of social groups set up for individuals with AS was obtained from the National Autistic Society and each of these was contacted with a view to sending information sheets out to its members. This provided a particularly fruitful method of recruitment – several volunteers were found, mainly from the Woking and Bristol social groups.

Controls were picked to be age, gender and (where possible) IQ matched with the AS group (see chapters 4, 5 and 6 for the exact group characteristics, which differed slightly between studies). Suitable volunteers were recruited either from databases of people who had taken part in earlier studies who had indicated that they would be willing to take part in more, from emails circulated around the Institute of Child Health (not including any departments working within the psychology or neuroscience fields) or from adverts on the gumtree website (www.gumtree.com, a popular site for finding casual work in London).

**Inclusion and exclusion criteria**

For ethical reasons, all subjects were at least 18 years of age. AS subjects were required to have a diagnosis from a UK psychiatrist or psychologist. Diagnosis was confirmed using the autism diagnostic observation schedule (Lord et al., 1989; Lord et al., 2000, ADOS, see below for details); to be included, an individual had to score above cut-off for at least autistic-spectrum disorder (the wider autism phenotype). A parental diagnostic interview, such as the ADI-R (Lord et al., 1994) or 3-DI (Skuse et al., 2004), was not used because, for many of our participants, a reliable parental informant was unavailable (mean age of subjects was ~35 years, range 18 – 62 years). In order to further quantify
autistic symptomology in our sample, the autistic-spectrum quotient (AQ, Baron-Cohen et al., 2001b) was administered to the participants (see below for details). For both groups, individuals were excluded if they had a history of neurological or psychiatric disorder other than that under study. For AS subjects this was relaxed in relation to anxiety and depression, which were felt to be unavoidable comorbid conditions (Gillott et al., 2001; Gillott and Standen, 2004; Stewart et al., 2006; Weisbrot et al., 2005).

**ADOS**

The ADOS is a semi-structured, standardised assessment of social interaction, communication and imaginative use of materials for individuals suspected of having an ASD (Lord et al., 2000). It consists of four 30-minute modules, each designed to be administered to different individuals according to their level of expressive language. In the case of the present thesis, this was always module 4, designed for adults or adolescents with fluent speech. This module consists of an interview section, during which both socioemotional questions and questions about daily living are asked. There are also a number of tasks, such as describing a picture, which tap into imaginative abilities.

The ADOS interviews were conducted and marked by a trained examiner, Rebecca Chilvers, to whom I am grateful. Interviews took place in a quiet room and were filmed for later off-line assessment. The ADOS algorithm for DSM-IV/ICD-10 diagnosis (Lord et al., 1999) was used to classify individuals as 'autistic', 'autistic spectrum' or 'below cut-off'. Individuals below cut-off were excluded from the study. Classification is made on the basis of exceeding thresholds on each of two domains: reciprocal social interaction
and communication, and exceeding a threshold for a combined social-communication total.

**Autistic-spectrum quotient**

The autistic-spectrum quotient (AQ) is a brief, self-administered instrument for measuring the degree to which an adult with normal intelligence has the traits associated with the autistic spectrum (Baron-Cohen et al., 2001b). It comprises of 50 questions, made up of 10 questions assessing 5 different areas of autistic symptomology: social skill, attention switching, attention to detail, communication and imagination. Baron-Cohen et al. (2001b) report that a group of 58 adults with AS or high-functioning autism had a mean score of 35.8 (SD = 6.5), whereas a sample of 174 randomly selected controls had a mean score of 16.4 (SD = 6.3). In addition, 80% of the adults with AS or high-functioning autism scored ≥ 32, compared to 2% of controls.

**Neuropsychological tests**

**IQ measures**

As a measure of IQ, I used the Wechsler Abbreviated Scale of Intelligence (WASI, Psychological Corporation, 1999). The WASI gives good concordance with the longer Weschler Adult Intelligence Scale (Psychological Corporation, 1997) from which it was developed, but is much quicker to administer, usually taking 30 minutes or less. The WASI consists of four subtests: Vocabulary, Block Design, Similarities and Matrix Reasoning. Results from the first and the third of these are combined to give a measure of
‘Verbal IQ’, whereas the second and the fourth give a ‘Performance IQ’ measure. A combination of all four gives a ‘Full scale IQ’ score.

**Developmental test of visual perception**

Although the performance IQ subsets of the WASI are thought to measure aspects of visuo-spatial ability (Psychological Corporation, 1999), it was felt that a more direct test of visual-perceptual skills should be taken to rule out the possibility that poor fear recognition was related to deficits in this domain. To this end, in chapter 4 I administered the Developmental Test of Visual Perception (DTVP, Reynolds et al., 2002). This battery is thought to provide a purer test of visual perceptual skill than the performance IQ subtests of the WASI as it is as divorced as possible from reasoning ability (Reynolds et al., 2002).

**Revised NEO Personality Inventory**

In chapters 3 and 5 I am interested in characterising subjects’ personality. The instrument I have chosen for this is the Revised NEO Personality Inventory (NEO PI-R, Costa and McCrae, 1991). The NEO PI-R was developed to operationalise the classic five-factor model of personality, the structure of which has emerged from the last four decades of research (Digman, 1990). The five factors represent the most basic dimensions underlying the traits identified in both natural languages and psychological questionnaires. They are: ‘neuroticism’, ‘extraversion’, openness to experience’, ‘agreeableness’ and ‘conscientiousness’. Each of the five factors is made up of six intercorrelated traits known as *facets*, which offer a more fine grained analysis of personality. For example, ‘neuroticism’ comprises the following facets: ‘anxiety’, ‘angry hostility’, ‘depression’,
self-consciousness', 'impulsiveness', and 'vulnerability'. There are eight questions for each facet, making 48 for each factor and 240 in total. The instrument takes approximately 40 minutes to complete.

Anxiety measures

As well as personality, in chapters 2 and 5 I measure the level of anxiety experienced by the participants. I am interested in both general anxiety and also in the specific case of anxiety in social situations. For the former I used the trait portion of the Spielberger State-Trait Anxiety Inventory (Spielberger, 1983) and, for the latter, the Social Phobia and Anxiety Inventory (Turner et al., 1999).

Trait portion of the State-Trait Anxiety Inventory

Trait anxiety refers to relatively stable individual differences in anxiety-proneness, that is, to differences between people in their tendency to perceive stressful situations as dangerous or threatening and to respond to such situations with elevations in the intensity of their state anxiety (Spielberger, 1983). The trait portion of the state-trait anxiety inventory is a self-report questionnaire of twenty items. Scores are transformed into T-scores taking into account the age of the person being examined.

Social-Phobia and Anxiety Inventory

The Social Phobia and Anxiety Inventory (SPAI, Turner et al., 1999) is an empirically derived self-report inventory specifically developed for social phobia and anxiety. It assesses the somatic, cognitive and behavioural aspects of social anxiety across a wide
range of social situations and settings. It contains 45 items arranged in a Likert scale format, allowing for an assessment of symptom severity.

**Marlowe-Crowne Social Desirability Scale**

Factors such as faking or response bias can diminish the validity of self-report questionnaires (Cronbach, 1990; Greenwald et al., 2002). In anxiety measures, a prominent form of response bias is social desirability, i.e. the tendency to portray oneself in a positive light, which can lead to a substantial underestimation of an individual’s true value on these dimensions (Egloff and Schmukle, 2003). To control for this, it is common practice in anxiety research to attempt to measure the propensity for social desirability and to use it as a covariate in statistical analyses where appropriate. To this end, wherever I take an anxiety measure I also administer the Marlowe-Crowne Social Desirability Scale (SDS, Crowne and Marlowe, 1960). The SDS consists of 33 questions, drawn from a population of items defined by behaviours which are culturally sanctioned and approved but which are improbable of occurrence. Participants decide ‘true’ or ‘false’ depending on whether or not they believe themselves to engage in the behaviour. The resulting score is an index of the tendency to portray oneself in a good light.

**Ekman-Friesen Test of Facial Affect Recognition**

The photographs of emotional expressions used in this test were produced using the FACS system, discussed in chapter 1 (Ekman and Friesen, 1978). The pictures have been validated by numerous samples from a wide variety of cultural backgrounds, including groups of previously isolated peoples, such as the Dani of West New Guinea (Ekman and Friesen, 1971). Furthermore, as discussed in chapter 1, the photographs have been used in
countless neuroimaging experiments and reliably activate brain areas known to be involved in social and emotional processing, such as the amygdala, MPfC and STG (e.g. Morris et al., 1996; Winston et al., 2003a; Winston et al., 2004). In addition, the test has been used with numerous samples of psychiatric and neurological patients, allowing direct comparison between my data and these populations.

The exact procedure and presentation of the test differed slightly between the experiments – these details are given in the relevant results chapters. In each case, however, certain factors were constant. Subjects viewed 60 halftone photographs, 10 exemplars of each of the 6 basic emotions (happiness, sadness, fear, surprise, anger and disgust). Subjects were shown the six emotion labels and were told to “pick the one that best fits what you think the person is feeling”. Before beginning the experiment, subjects completed 6 practice examples, one for each emotion. Feedback was not given on these items, the stimuli were not used in the subsequent test and responses to them were not analysed. The dependent variables were the number of correctly identified examples for each of the six emotions.

**Frith-Happé theory of mind task**

**Background**

This animated task was chosen as a measure of ToM ability. It has been clinically validated in studies of ASD children (Abell et al., 2000) and adults (Castelli et al., 2000; Castelli et al., 2002). In normal individuals, the task recruits the posterior STG, the TP and the MPfC – brain areas consistently activated during ToM reasoning (for review, see Gallagher and Frith, 2003). One advantage of the Frith-Happé task is that it is sensitive
enough to measure deficits in high-functioning individuals, who would have no difficulty in passing traditional ToM tasks (Frith et al., 1994). Another advantage is that the stimuli are perceptually very simple and removed from the human context: it does not require the perception of social cues from the face for example. In this sense it is a somewhat 'purer' test of mentalising ability than other tasks designed for high-functioning individuals, such as the 'reading the mind from the eyes' task (Baron-Cohen et al., 2001a).

Procedure

Eight silent cartoons, each featuring a large red triangle and a smaller blue triangle, were shown on a computer screen. Each animation lasted between 34 and 45 seconds. There were two conditions, with four animations in each condition. In one type of animation, the actions of one character responded simply to those of the other. Animations of this type of action are intended to elicit goal directed action descriptions (e.g. following, fighting) and thus will be referred to as 'Goal Directed' (GD) animations. The ‘scripts’ of the GD cartoons involved the triangles chasing each other, following each other, fighting with each other and dancing with each other. The second type of cartoon, by contrast, showed one character reacting to the other character's mental state. This type of action pattern is intended to elicit more mental-state (theory of mind) descriptions (e.g. mocking, coaxing) and will hereafter be referred to as ‘Theory of Mind’ (ToM) animations. The ‘scripts’ to the ToM cartoons involved the triangles persuading, surprising, mocking and seducing each other (see Abell et al., 2000, for more details).

Participants were read the task instructions (Castelli et al., 2000; Castelli et al., 2002) asking them to describe what they thought the triangles were doing. The animations were shown in a random order. Participants’ spoken responses were recorded, transcribed and
scored. Following Castelli et al. (2000, 2002), responses to each animation were scored on three dimensions: *Intentionality* (degree of intentional attribution, range 0-5, with absence of intentional language at one extreme and elaborate use at the other), * Appropriateness* (range 0-2), with incorrect at one extreme and highly appropriate at the other and *Length* of description (0-4, ranging from no response to four or more clauses). Responses were scored by two trained raters who were blind to NFS / LFS group membership. Where there was discrepancy between raters, the item was discussed and a compromise score was agreed upon.

**Psychophysiological measurements**

In chapters 3, 4 and 5, I use eyetracking technology to monitor subjects’ gaze fixation patterns. In chapter 4 and 5, I measure skin conductance responses as an index of autonomic arousal. These are described in detail below.

**Eyetracking**

*Background*

Detailed visual information can be obtained only through the fovea, therefore the eyes must move in order to provide information about any object or scene which is to be inspected in detail (Norton and Stark, 1971). Measuring eye gaze fixations (points in the visual field which are foveated for at least 100ms) has therefore been used extensively in psychology as an indicator of which parts of a visual stimulus a person is attending to (e.g. Adolphs et al., 2005; Keating and Keating, 1982; Norton and Stark, 1971; Walkersmith et al., 1977). I use this technique in chapters 3, 4 and 5 to measure the attention paid to the eye region of faces. Below, I describe the theory behind the technique, plus give details
of the set-up and experimental procedure used to produce the results given in later chapters.

**Theory of measurement**

A beam of infra-red light illuminates the eye and its image is captured using a video camera. Two bright circular areas are apparent in the image – one corresponds to the pupil and the other to the reflection of the illuminator from the front surface of the cornea (the corneal reflection or CR). Using the fact that these features are usually the brightest in the image, plus some prior information on their likely size, shape and smoothness, the system is able to identify the centre of both the pupil and CR. The distance and direction of the separation between the pupil and the CR varies with eye rotation (change in point of gaze) but does not vary significantly with eye translation (head movement with respect to the eye camera). A change in pupil-CR separation is therefore proportional to the change in point of gaze. By first using a calibration procedure, which measures pupil-CR separation at several known points on a screen, it is possible to calculate where on that screen the person is fixating with an error of less than one degree of visual angle.

**Data acquisition**

An ASL (Applied Science Laboratories) Model 504 remote infrared pupil-corneal reflection eye tracker (ASL 2001) was used to measure the participants' line of gaze on the fixed image shown. The eye tracker was linked to a host computer (Dell Workstation Precision 650) which served as a digital data-recording device, and an auxiliary video display unit for observing the monitored eye. The stimulus scene was visible from the
tester's sitting position. Retinal and CR produced by the infrared reflection were sampled and transmitted to the host computer for recording at 120 Hz.

**Experimental task and procedure**

The assessment took part in a darkened and sound-proof room. Participants were seated in a comfortable chair in front of the computer monitor and were asked to place their chin on a padded chin rest. The chin rest was provided to minimise head movements, thus maximising the accuracy of the eye tracking, and to ensure a stable distance of 80 cm between the subject and the centre of the stimulus display screen. The task was divided into two phases, with a break in between the two during which the subject was allowed to move around. At the beginning of each phase, a brief calibration procedure took place, during which subjects were asked to look at nine points of known position on the screen. This allowed for individual differences in head and seating position.

The experiment was realised using Cogent 2000 (http://www.vislab.ucl.ac.uk/Cogent/), which is a MatLab toolbox, designed for creating psychological experiments. The stimuli used were 60 high-resolution monochrome digital photographs from Ekman and Friesen’s (1976) “pictures of facial affect”, consisting of 10 exemplars each of the 6 ‘basic’ emotions: happiness, sadness, fear, surprise, anger and disgust. These were the same pictures that were used in the on-line Ekman-Friesen test of facial affect recognition, described above. Each image was shown on a 43 cm computer monitor. In phase 1 of the experiment, participants were shown the images in a randomised order, with the constraint that no emotion was shown more than twice in a row. Images were presented for 2500 ms, preceded by a central fixation cross for 1500ms and followed by a blank grey screen for 500ms (total ISI = 2000ms). Participants were instructed to fixate the
cross and then to look at the face, “however they wanted to”. In the second phase, the participants were again shown the 60 faces but this time the images were in the standardised order used in the Ekman-Friesen test of facial affect recognition. Again, each face was presented for 2500 ms, preceded by a central fixation cross for 1500ms and followed by a blank grey screen. This time, however, following the presentation of each face the participants were asked to decide which emotion had been expressed. The emotion labels appeared on the screen following each facial image and were numbered 1-6. Subjects responded via a key press and had an unlimited time to answer.

Data analysis

Any trials showing loss of tracking integrity and off screen gazes were excluded from subsequent data analysis. The regions of interest, the eye and mouth areas of the face, were predefined for each face. The number of fixations made in these regions and on the face as a whole during the 2500ms presentation was calculated. A fixation was defined as a set of consecutive gaze coordinates, confined within a diameter of 1 degree of visual angle for a duration of 100 milliseconds or more (Norton and Stark, 1971). The fixations for the eyes and mouth as a percentage of total fixations on the face for each presented stimulus were calculated. The average proportions of total fixations for the eye and mouth region were calculated for each emotion for each subject.

Autonomic responses – electrodermal activity

Background

The use of electrodermal activity (EDA) as a psychophysiological measure dates back to 1888 when Féré discovered momentary increases in skin conductance in response to a
variety of stimuli. Today, these changes are known to reflect the engagement of the sympathetic branch of the autonomic nervous system (see below) and a distinction is made between tonic and phasic measurements. The tonic level of skin conductance is the absolute level of conductance at any given moment in the absence of a measurable phasic response, and it is referred to as the skin conductance level (SCL). Superimposed on the tonic level are phasic increases in conductance, known as skin conductance responses (SCRs).

SCRs are elicited by almost any novel, unexpected, potentially important, discrete stimulus in the environment (Siddle, 1991). Amplitude is the most commonly measured feature of an SCR, and this is known to be heightened by increases in stimulus significance and stimulus intensity (Dawson et al., 2000). As such, SCR amplitude provides a good indicator of the social or emotional impact that a stimulus has on a person.

I chose electrodermal activity as my measure of autonomic arousal largely because of its ease of measurement, quantification and analysis compared to the alternatives, such as heart-rate and pupilometry. In particular, I rejected pupilometry because of the difficulty in equalising the brightness of stimuli, necessary to avoid the confound of luminance-induced changes in pupil diameter. Heart-rate would have been a reasonable alternative. However, apart from being slightly more difficult to measure and analyse, Fowles (1988) has argued that heart-rate is influenced primarily by the engagement of a behavioural ‘activation system’ that is involved in responding during appetitive reward seeking and during active avoidance. EDA, on the other hand, is viewed as an ‘anxiety system’, responding to such situations as punishment and passive avoidance. Given that I am
mostly interested in the anxiety- rather than reward-like arousal properties of the various stimuli I present, electrodermal activity seemed the more appropriate measure.

I provide SCR data in chapter 5 to measure the arousal produced by viewing direct gaze and in chapter 6 to measure the arousal produced by emotional words. The precise details of experimental procedure differ in each instance and are given in the relevant chapters. Here I will report the experimental set-up and data analysis techniques common to both experiments, but first I will briefly review the physiological basis of EDA and SCRs.

Physiological basis

The palmar and plantar surfaces of the hands and feet have a high density of eccrine sweat glands, the functions of which appear to be both thermoregulatory and as an aid to grasping behaviour (Edelberg, 1972). Activation of these sweat glands provides a conductive path through the relatively resistant corneum of the epidermis. As more sweat is produced the resistance in the corneum is reduced, producing an observable change in electrodermal activity.

Eccrine sweat glands are innervated by sympathetic cholinergic fibres originating in the sympathetic chain (Dawson et al., 2000). Importantly, there is no parasympathetic control of EDA, meaning that changes in eccrine sweat gland activity can be regarding as a pure indicator of sympathetic activity. The validity of using EDA as an indirect measure of this has been proven experimentally: there is a high correlation between bursts of sympathetic nerve activity and SCRs (Wallin, 1981).
Excitatory and inhibitory influences on the sympathetic nervous system are distributed in various parts of the brain, so the neural mechanisms and pathways involved in central control of EDA are numerous and complex (for review, see Boucsein, 1992). However, animal studies have implicated the amygdala in producing EDA associated with affective processing and numerous neuroimaging experiments show a correlation between amygdala activity and the amplitude of SCRs in response to emotional stimuli (Williams et al., 2005) confirming that SCRs are a viable measure of stimulus arousal.

Data acquisition and analysis

SCRs were collected via a pair of silver-silver chloride electrodes, approximately 0.8 cm$^2$ in contact area and filled with 0.05 M sodium chloride gel, placed on the volar surfaces of the distal phalanges of digits II and III of the non-dominant hand after the skin was wiped with an alcohol swab. Data were recorded and analysed using a complete system provided by Psylab (www.psylab.com). MatLab interfaced with the Psylab system via the parallel port, allowing synchronisation of SCR recording with the experimental paradigm. SCRs beginning 1 – 4 seconds after stimulus onset were detected automatically by Psylab software and their amplitude recorded for further off-line analysis (see chapters 4 and 6 for further details).

Neurophysiological and neuroanatomical measurements - MRI

I use magnetic resonance imaging (MRI) of the brain in two experiments presented in this thesis. In chapter 3, I use functional MRI (fMRI) to investigate brain activity in response to direct gaze, comparing responses in two groups of normal individuals: those who are
good at recognising fear from facial expressions and those who are poor at this. In chapter 5, I use structural MRI to investigate brain morphology changes associated with AS.

A full treatment of MRI methodology would run to many hundreds of pages. Here, I will briefly describe the following points: the basic physics of the MRI signal, the physiology of the blood oxygenation level dependent (BOLD) response and the analysis of fMRI and structural MRI, including spatial pre-processing as well as statistical analysis.

**Basic principles of MRI**

*The MRI signal*  

The MRI signal is based on the magnetic properties of atoms which have an odd number of protons in their nucleus (e.g. $^1$H, $^{13}$C). Such nuclei are said to have nuclear ‘spin’ and, when placed in a magnetic field, behave as magnetic dipoles that can assume two energy states: a high energy state (oriented against the magnetic field) or a low energy state (aligned with the magnetic field). Transition from the low to the high energy state is associated with the absorption of energy in the radiofrequency (rf) range, whereas transition from high to low energy state results in the emission of rf energy. In MRI, a large homogenous magnetic field, produced by the imaging magnetic, causes the majority of spins to align with the magnetic field. Small magnetic field gradients, produced via an rf pulse, are then superimposed onto the homogenous field, tipping the spins against the main magnetic field so that they assume the high energy state. On removal of the small

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8 This section is based largely on information from two textbooks - *Functional MRI: an introduction to methods* (Jezzard et al., 2001) and *MRI: the basics* (Hashemi and Bradley, 1997).
field gradient, the spins relax back to the low energy state emitting rf energy as they do so – this is the MRI signal.

**Generating contrast in MRI**

The majority of the MRI signal *in vivo* comes from the hydrogen atoms that make up water in tissue. Variations in the relative concentrations of water protons provide contrast between some structures, allowing clear discrimination between bone (little water, low MR signal) and brain (approximately 70% water, high signal), for example. Further contrast between different tissue types is possible because the time it takes for the nuclear spins of hydrogen atoms to relax differs depending on features of the local environment. This is governed by a ‘spin lattice’ relaxation process that has a rate constant 1/T1, where T1 is the so called ‘spin-lattice relaxation time’. T1 for hydrogen atoms in the body depends on the type of tissue containing the relevant water molecules. For example, the relaxation time of protons in cerebrospinal fluid, which is close to pure water, is much slower than that of protons in grey matter. By varying the repeat time between rf pulses, the contrast between tissue regions of long and short T1 can be altered dramatically.

In MRI, one is observing emissions from huge numbers of spins simultaneously. On a molecular level these nuclei are each experiencing continuous very small changes in magnetic field, allowing an exchange of energy between the nuclei which leads to a loss of coherence in the phases of their resonance emissions. This loss of coherence leads to an exponential loss of intensity for the summed resonance signal from all the nuclei together, described by the ‘spin-spin’ or T2 relaxation time. The T2 is an intrinsic property of nuclei in a particular chemical environment and therefore provides another
source of contrast for distinguishing different tissue types. Grey matter, for example, has a longer T2 than white matter.

A third source of contrast arises when there are local magnetic field inhomogeneities that molecules can diffuse through. As molecules move into regions of different local fields, their resonance frequencies change slightly, lowering the coherence of the nuclear spins. This leads to a more rapid decay of the net signal, expressed by the T2* relaxation time.

Contrast differences arising from differences in relaxation times are realised by altering aspects of the rf pulse sequences with which the spins are excited. In this way it is possible to tune the scan to the aspects of the tissue that one wants to image.

**fMRI**

*Physics and physiology*

**Haemodynamic changes and the blood oxygenation level dependent response**

For a long time, it has been known that neural activity is associated with increases in local blood flow. For example, as far back as 1888 an Italian physician, Angelo Mosso, recorded the pulsations of the cortex in patients with skull defects, noting that the pulsations increased regionally with specific mental activities (Mosso, 1881). The purpose of this increase in blood flow is to deliver oxygen and glucose to the active region, necessary for the increased energy utilisation resulting from increased neural activity. However, despite over 100 years of research, the precise way that neural activity links to energy metabolism and how this causes increased blood flow remains unclear. It is hypothesised that increased energy utilisation occurs at the synapse (Duncan et al.,
1987; Duncan and Stumpf, 1991), with metabolic changes in adjacent astrocytes during re-uptake of glutamate thought to play a prominent role (Magistretti and Pellerin, 1996). Astrocytes may respond to increased metabolism by dilating blood vessels, thereby increasing the flow and supply of oxyhaemoglobin (Magistretti and Pellerin, 1999).

In fMRI, neural activity is inferred by measuring the amount of oxy- relative to deoxyhaemoglobin in the blood. This is possible because deoxyhaemoglobin is paramagnetic, due to its central iron particle with four unpaired electrons (Pauling and Coryell, 1936). As a result, the magnetic susceptibility of blood depends upon the ratio of oxy- to deoxyhaemoglobin (this is the blood oxygen dependency that gives BOLD its name).

Protons in water molecules within the blood will experience local field inhomogeneities as a result of the levels of deoxyhaemoglobin. These inhomogeneities are detectable as a change in the $T_2^*$ relaxation time: areas of low oxygenation (high deoxyhaemoglobin) have increased inhomogeneities, resulting in lower $T_2^*$ and less MRI signal. Sensitivity of MRI to BOLD is maximised by using a sequence sensitive to these microscopic changes in $T_2^*$. The feasibility of BOLD fMRI was demonstrated first in animal models (Ogawa et al., 1990) and subsequently in humans (Frahm et al., 1992; Ogawa et al., 1992).

**Analysis**

The fMRI experiment reported in chapter 3 is analysed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/), a suite of functions designed for use within MatLab (Mathworks Inc, Nantick MA). Before statistical analysis, images are first realigned, normalised and then smoothed, as described below.
Spatial Realignment

Head movements within the scanner can cause artefacts in the BOLD signal which have striking similarity to the BOLD signal produced by performance of a cognitive task (Hajnal et al., 1994). Spatial realignment controls for this artefact by estimating and correcting for the degree of head movement from scan to scan over an fMRI time series. In SPM2, each volume is compared to a reference volume (the first in experiments described in this thesis) and parameters estimated for six transformations (x, y and z translations and rotations in the three principal axes). The implementation involves iteratively comparing transformations to minimise the mean squared difference between the current image and the reference (Friston et al., 1995a).

Even after volumes are spatially realigned, subjects' movements during data acquisition might have introduced artefactual variance into the time series. This is adjusted for mathematically, based on a moving average auto regression model of spin-excitation history effects.

Spatial normalisation

Spatial normalisation of fMRI time series renders the volumes into a common anatomical space. This allows statistical inference about a group of subjects, as well as comparison of results between different experiments. The anatomical space adopted in SPM is that of the template brain from the Montreal Neurological Institute, derived from 305 brains. It approximates the space described in Talairach and Tournoux’s (1988) atlas. The approach adopted in SPM (Friston et al., 1995a) consists of two components aimed at minimising the differences between the image to be normalised and an image in the anatomical space to be normalised to (the 'template' image). Firstly, parameters are
estimated for 12 affine transformations – 3 translations (x, y and z), 3 rotations, 3 shears and 3 zooms. Secondly, parameters are estimated for a series of non-linear ‘warps’ or deformations. A Bayesian estimation framework, implemented iteratively, is used to optimise the normalisation procedure. In the study described in chapter 3, the template image used for normalisation was the EPI template provided with the SPM package.

**Spatial smoothing**

Following realignment and normalisation, images are smoothed with a Gaussian kernel. This is important for a number of reasons. Firstly, it increases the signal to noise ratio. Secondly, central limit theorem implies that the distribution of errors resulting from smoothed data will be more normal, helping to ensure the validity of parametric tests. Finally, smoothing the data reduces inter-subject anatomical and functional-anatomical differences that remain after normalisation.

**Statistical analysis in SPM**

SPM uses a mass univariate approach to analyse fMRI data. A model of hypothesised effects is built, based on the experimental design used. At each voxel of the brain, specific effects are examined by testing the fit of the model using a contrast pertaining to a possible effect (Friston et al., 1995b). Maps of t or F statistics are thus created (statistical parametric maps or SPMs) allowing a test of an experimental hypothesis against the null hypothesis of no effect. In SPM, parametric statistics are used to draw inference. This means that the statistics used have a known distribution and the probability of obtaining a particular statistical result is easily tested against this distribution.
More specific details of how the data in chapter 3 were analysed are given in that chapter's methods section.

**Structural MRI**

*Different approaches – pros and cons*

There are two major approaches to investigating brain morphometry: (semi)-manual methods, which involve using anatomical landmarks to trace around and then measure the volume of brain structures in native space, and automated methods, which require images from multiple subjects to be registered together by some kind of normalisation procedure, therefore allowing automatic region-by-region analysis by a computer. Of the latter methods, the most commonly used is voxel based morphometry (VBM, described below), but a number of related methods also exist, including tensor-based morphometry and deformation based morphometry (Ashburner and Friston, 2004).

There are numerous advantages and disadvantages to both manual and automated methods. The major advantage of manual techniques is that volumetric measurement is conducted on the native structural images, avoiding the problems of normalisation inherent in automated schemes. In addition, manual tracing leads to easily interpretable results – data are volume measurements in clearly understandable units (e.g. cm$^3$). However, it requires a specific region of interest to be defined *a priori*. As well as being a disadvantage in itself, this also means that, in practice, only clearly definable structures (e.g. the hippocampi or ventricles) can be investigated. Even for the structures just mentioned, identifying brain regions with consistency is no easy task and requires both considerable time and expertise. Different methods exist for identifying even well defined
structures, leading to variability between different studies - see, for example, the comments by Dziobek et al. (2006) regarding the variability in amygdala volumes reported by different manual tracing studies. Finally, even when skilled raters use the same method to identify structures, residual variability remains.

By comparison, automated methods such as VBM are fast, simple to use and objective, thereby circumventing many of the disadvantages of manual tracing methods. In particular, they do not require a hypothesis and enable regional comparisons throughout the whole brain without restrictions to a few selected areas. Their principal drawbacks relate to the need to spatially pre-process the images, rather than working with the native scans. Images are first spatially normalised into the same stereotaxic space (by registering them with a template) before being segmented into different tissue classes (grey matter, white matter and cerebro-spinal fluid, or CSF). Algorithms of this kind will inherently introduce some noise and artefact into the data. A specific problem occurs when comparing the brains of a special population (with a particular disease for instance) with a normal control sample. The templates used for normalisation are typically derived from samples of normal individuals, meaning that normalisation could be biased towards controls. A way around this is to use a custom template, derived from the population under study. However, to be accurate such a template would need to be constructed from data from many subjects, which in many cases is impractical (see John Asburner’s discussion of this issue at http://en.wikibooks.org/wiki/SPM-VBM).

The choice of method usually depends on the nature of the study and on the local availability of expertise. Where there is no \textit{a priori} hypothesis leading to specific regions of interest or where the sample size is likely to be very large, automated techniques hold clear advantages. When the intention is to investigate certain, well defined brain
structures, the advantages are less clear and researchers often choose manual tracing techniques to avoid the problems of spatial pre-processing. The study described in chapter 5 of this thesis makes clear hypotheses regarding amygdala volume. However, given the expertise available in my unit, it was felt that an automated method would give more robust results. Voxel-based morphometry was the obvious choice as it is the most tried and tested method and there exists considerable local expertise in this technique.

**Voxel-based morphometry**

VBM produces statistical parametric maps (SPMs) of volumetric differences. The technique typically involves the following steps (Ashburner and Friston, 2004):

- *Spatial normalisation* of the images to the same stereotaxic space via registration of the image to the same template. The method used to do this is often the same as that described above for normalisation of fMRI images (but see below).

- *Segmentation* of the normalised images into different tissue classes. Classically, this began by registering the images to be segmented with a tissue probability map, derived from a large sample of brains. After registration, these maps represent the prior probability of different tissue classes being found at each location in an image. Bayes rule is then employed to combine these priors with tissue type probabilities derived from voxel intensities to provide the posterior probability. The most recent version of the SPM software (SPM5) has made improvements to the segmentation function, which are described below.
- **Modulation** of the images. Spatial normalisation results in the volumes of certain brain regions increasing whereas others decrease. This has implications for what VBM actually tests. The objective of VBM is to identify regional differences in the amount of a particular tissue (usually grey matter). To preserve the actual amounts of grey matter within each structure, a further processing step (known as modulation) is incorporated. This multiplies the partitioned images by the relative voxel volumes. Without this adjustment, VBM can be thought of as comparing the relative concentration of grey matter. With this adjustment, VBM compares the absolute amount of grey matter in different regions.

- **Smoothing** of the images by convolving with an isotropic Gaussian kernel. This makes the subsequent voxel by voxel analysis comparable to a region of interest approach because each voxel in the smoothed images contains the average amount of grey matter from around the voxel (where the region around the voxel is defined by the form of the smoothing kernel). As with fMRI data, smoothing also has the effect of rendering the data more normally distributed, increasing the validity of using parametric statistical tests. The size of the smoothing kernel is usually chosen to be comparable to the size of the expected regional differences, thereby sensitising the analysis to differences at this spatial scale (by the matched filter theorem).

- Data are now analysed via voxel-wise statistical tests, using the general linear model, as was described for fMRI data. The result is a SPM showing, for example, regional differences between two groups or regions where grey matter volume correlates with another measure (such as disease severity). As with fMRI data, where there is no *a priori* hypothesis, corrections for multiple dependent comparisons are made using Gaussian random field theory. Where there is a hypothesis there are two options,
either ‘small volume corrections’ are made, centering on the region of interest, or a
stringent but uncorrected threshold (typically \( p < .001 \)) is used.

Recently, a form of VBM analysis known as ‘optimised’ VBM (Good et al., 2001) has
become popular. This involves a tweak in the normalisation step where, rather than
matching to a whole brain template, grey matter is matched to a grey matter specific
template. This improved normalisation by reducing the confounding effects of non-brain
(e.g. scalp) structural variability on the registration. However, with the advent of the new
version of SPM (SPM5) ‘optimised’ VBM is no longer necessary because of
improvements to the segmentation function, described below.

**Unified segmentation in SPM5**

The classical method of VBM segmentation was inherently circular, because the
registration required an initial tissue classification, and the tissue classification requires
an initial registration. In the latest version of SPM, this circularity has been resolved by
combining both components into a single generative model. Estimating the model
parameters (for a maximum \( a \ posteriori \) solution) involves alternating among
classification, bias correction and registration steps. This approach, described in detail by
Ashburner and Friston (2005), provides better results than simple serial applications of
each component and removes the need for an ‘optimised’ VBM strategy.
**VBM in this thesis**

In chapter 5 I report an experiment which used VBM to compare amygdala volumes between individuals with AS and matched controls as well as correlating amygdala volume in AS with various measures, such as eye fixation pattern and fear recognition score. I thereby test predictions of the hyper- and hypo-active amygdala models of ASD (see chapter 1). VBM analysis was conducted using SPM5 using the methods described above. Given the focus of the investigation on the amygdala, Type I error was controlled via small volume correction, using MNI-derived anatomical templates of the left and right amygdala to define the volume to be corrected by. The anatomical masks were created using WFU_PickAtlas (http://www.fmri.wfubmc.edu/download.htm). Specific details of the statistical tests performed are given in the methods section of chapter 5.
Chapter 3 - Poor fear recognition in normal males

Part 1 - Fear recognition ability predicts social-cognitive and neural functioning in males

Introduction and summary

To date, few studies have examined individual differences in social cognitive ability and linked these to underlying neural function. As part of a lab-wide study into the genetics of social cognition, the emotional expression recognition abilities of 341 adult males were examined. The majority of subjects performed at or near ceiling (mode scores were 9 or 10), but for the negative emotions (fear, sadness, disgust and anger) there was a considerable number who performed poorly (see figure 4 on page 111). This tail was most marked for fearful faces, where 8% of the sample showed fear recognition deficits akin to those reported in patients with amygdala damage.

A sample of 25 “low fear scoring” (LFS) and 25 “normal fear scoring” (NFS) males were brought into the lab for further testing. Despite an absence of psychological or neurological problems, on re-test LFS continued to show a significant fear recognition deficit. I hypothesised that low fear recognition ability would be related to reduced functional integrity of the amygdala and associated regions of the social brain (namely, the FG, STG, TP and MPFC). Thus, for ‘low fear scorers’ (LFS) compared to “normal fear scorers” (NFS), I predicted deficits on a test on ToM abilities (the Frith-Happé

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9 An additional aim of the original project, unrelated to this thesis, was to investigate the possible influence of X-linked genes on emotion recognition ability. This is technically simpler with males (who only have one X chromosome) than females, therefore only males were invited to take part in the study.
triangles task) – a social-cognitive task known to involve these brain regions (Castelli et al., 2000; Schultz et al., 2003). As predicted, LFS made fewer and less appropriate mental state attributions to the cartoons than did NFS.

I also predicted that, compared to NFS, LFS would show reduced activation of the amygdala and associated brain regions when processing socially relevant stimuli. I tested this by comparing neural activation evoked by faces with high social significance (direct gaze) to that evoked by faces with lower social significance (averted gaze). My reasoning for manipulating social significance by altering eye gaze rather than by altering emotional expression was that, because the subject groups had been selected on the basis of differences in fear recognition abilities, any difference in response to another socially relevant dimension of the face would provide a more stringent test of my hypotheses. Also, as discussed in chapter 1, faces with direct gaze are known to engage diffuse areas of the social brain, including the ToM network. As predicted, LFS demonstrated significantly reduced activation in the amygdala, FG and anterior STG when viewing faces with direct versus averted gaze. In a functional connectivity analysis, NFS showed enhanced connectivity between the amygdala and anterior STG in the context of direct gaze; this enhanced coupling was absent in LFS.\(^\text{10}\)

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\(^{10}\) Some of the work presented in this chapter has recently been published in the *Journal of Cognitive Neuroscience* (Corden et al., 2006).
Methods

Population study

An email was circulated to each department of University College London, asking students and staff to participate in an on-line psychology experiment. A prize of £500 was offered as an incentive. In this on-line version of the Ekman-Friesen test of facial affect recognition (described in chapter 2), the six emotion labels were presented adjacent to each image and subjects indicated their responses via a mouse click. There was an unlimited time to answer.

Male subjects were classified according to their performance at recognising fearful expressions. Participants scoring 5/10 or less (8% of the sample) were labelled as LFS. This cut-off was chosen because it encompasses a range of scores usually reported for patients with amygdala damage on similar tests (Broks et al., 1998; Calder et al., 1996; Young et al., 1996). The mean fear recognition score was 8.2/10; therefore individuals scoring greater than or equal to 8/10 were labelled as NFS. This dichotomous approach, using extremes of the population, was chosen in preference to a correlational approach in order to maximise the potential differences associated with variation in fear-recognition ability.

Neuropsychological examination

Twenty-five LFS volunteered to participate in further experiments and stratified randomisation was used to age-match 25 NFS volunteers (NFS, 30 ± 7.6 years; LFS, 31 ±
10.3 years, mean ± SD). None of the subjects had any history of psychological or neurological disorder, as measured by an in-house medical screening questionnaire.

The full scale IQ of each subject was estimated using the two-subset form of the Wechsler Abbreviated Scale of Intelligence (WASI). In addition subjects repeated the Ekman-Friesen test of facial affect recognition and were examined on the Frith-Happé ToM task (see chapter 2). The Ekman-Friesen test was exactly the same as the on-line version, except participants completed it in the laboratory.

Group differences in behavioural scores were tested using t tests or Mann-Whitney tests, as appropriate. Threshold significance was set at \( p < .05 \), corrected for multiple comparisons via the Bonferroni-Holm step-down method (Hochberg and Tamhane, 1987).

**Functional Imaging Experiment**

Twelve LFS and twelve NFS volunteers were randomly selected from the right-handed members of the earlier groups and provided written informed consent to take part in the fMRI study.

**Stimuli**

Stimuli, shown in figure 3, were selected from those used in a previous study (George et al., 2001) and consisted of images of 12 people (6 men and 6 women) portraying a neutral expression. Each individual was photographed in full-face frontal view and also with the head rotated toward the right by 30° and for each of these head views, there were 2 images, one with the subject looking straight at the camera and one with gaze averted at

\[113\]
30°. Each face was centered in the image frame so that the edge of the nose between the two eyes - where faces are usually fixated at first glance (Yarbus, 1967) - always fell in the same location for frontal faces and for deviated faces. Four additional stimuli were then generated for each face, representing mirror-images of those already obtained. There were a total of 96 images (48 direct gaze and 48 averted gaze).

![Direct Gaze Faces | Averted Gaze Faces](image)

**Figure 3.** Example stimuli used to compare neural activity induced by direct gaze compared to averted gaze. Identical sets of stimuli from 11 additional sitters were formed. Mirror images of each picture were created, producing double the number of stimuli.

**Task**

Subjects were required to make a gender judgment for each face via a button press. Each stimulus was presented for 700 msec with an inter-stimulus interval of 500 msec. A blocked presentation of stimuli was used. The eight subconditions of stimuli (i.e., the four main conditions further divided by mirror imaging of the stimuli) resulted in eight blocks of twelve stimuli. The blocks and stimuli within each block were presented in a different random order for each subject. Between each block, a blank screen was presented for 5498 msec. Before each block, a fixation cross (placed in the area of the screen midway between where the eyes appear for the face stimuli) was shown for 1000 msec.
fMRI data acquisition and pre-processing

A Siemens 1.5T Sonata system (Siemens, Erlangen, Germany) was used to acquire BOLD contrast-weighted echoplanar images (EPIs) for functional scans. Volumes, which consisted of 48 horizontal slices of 2mm thickness with a 1mm gap, were acquired continuously every 4.32s enabling whole brain coverage. In-plane resolution was 3 x 3mm. Each subject's head was mildly restrained within the headcoil to discourage movement. Response judgments were made during scanning with a buttonbox held in the right hand. The first six EPI volumes were discarded to allow for T1 equilibration effects. Functional datasets were then pre-processed using SPM2 (Wellcome Department of Imaging Neuroscience; [http://www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) on a Matlab platform (Mathworks Inc, Nantick MA) correcting for head movement by realignment and normalising the functional scans to an EPI template corresponding to the MNI reference brain in standard space. Normalised images were smoothed using an 8mm Gaussian kernel.

Statistical analysis

Data analyses were conducted using SPM2, applying a mass univariate general linear model (GLM and using a mixed effects two-level framework - see chapter 2). In individual subject analyses, each of the four main stimulus categories (averted gaze/deviated head, averted gaze/straight head, direct gaze/deviated head, direct gaze/straight head) were modeled separately by convolving a box-car function with a synthetic haemodynamic response function. A high-pass filter with a cut-off of 238 seconds was applied to remove low-frequency noise.
Subject-specific parameter estimates were calculated for each stimulus category at every voxel. Specific effects (e.g. direct gaze – averted gaze) were tested by applying linear contrasts to the parameter estimates for each block. Contrast images from each subject were entered into second-level (random effects) analyses. In the a priori regions of interest (see introduction and summary), statistical threshold was set at $p < .001$, uncorrected for multiple comparisons.

**Functional connectivity**

To investigate functional connectivity between amygdala and other brain regions in the context of direct gaze we tested for “psychophysiological interactions”. These are condition-dependent (e.g. direct versus averted gaze) changes in the co-variation of response between a reference brain region and other brain regions (Friston et al., 1997). Separately for each subject, values of adjusted responses to direct gaze faces relative to averted gaze were extracted from the voxel in left amygdala maximally activated in the direct – averted gaze contrast of the main analysis (maximal voxel: $x$-21, $y$-3, $z$-21). Using a specially developed routine in SPM2, the adjusted data were first deconvolved, and amygdala activity at the time of the direct gaze blocks extracted. The resulting condition-specific estimate of neuronal activity was then reconvolved with a synthetic haemodynamic response function. This procedure was repeated for the averted gaze blocks. The resulting regressors were entered as variables of interest into a separate analysis. Linear contrasts were applied to the parameter estimates for the regressors in order to identify regions where responses exhibited significant condition-dependent interactions with amygdala activity. This was done separately for each subject. The resulting contrast images were entered into a second-level (random effects) analysis in order to allow generalization to the population.
Results

Behavioural findings

Population study

There were 341 male respondents to the on-line Ekman-Friesen test. The mean age of the sample was 29.3 years, $SD = 8.86$ years.

Figure 4 displays the results of the on-line Ekman-Friesen test. Most subjects performed near ceiling (median and mode scores were either 9 or 10 for all emotions except sadness, where both were 8). However, there were still a considerable number of people who performed poorly, especially for the negative emotions (fear, sadness, disgust and anger); this variability was most marked for fearful faces.

![Figure 4. Box plot displaying the results of the on-line Ekman-Friesen test of facial affect recognition. Boxes show the median (black line) and the inter-quartile range (IQR, edges of boxes). Whiskers are 1.5 * IQR. Circles represent mild outliers (between 1.5 and 3 * IQR) and stars represent extreme outliers (> 3 * IQR).]
As explained earlier, for purposes of further study, the respondents were now labelled on
the basis of their fear recognition score – those scoring 5/10 (8% of the sample) were
labelled as LFS, those scoring at least 8/10 (69% of the sample) were labelled as NFS
(see figure 5a).

Of the 25 LFS and 25 NFS who took part in further experiments, reaction times for fear
responses were very similar between groups – LFS: (mean ± SD) 925 ± 332 msec; NFS:
958 ± 384 msec; t(48) = -0.33, p = .74 – suggesting that differences in fear recognition
were not due to a speed-accuracy trade-off. Milder impairments in the responses of LFS
were apparent in the recognition of sad and angry facial expressions (see figure 5b).

**Neuropsychological tests**

The age-matched sub-samples of 25 LFS and 25 NFS were brought into the laboratory
and re-tested on their ability to correctly identify emotional expressions, as well as
undertaking a test of ‘mentalising’ ability. The IQs of the two groups did not differ
significantly: mean ± SD, LFS 117 ± 10.2; NFS 121 ± 8.5; t(48) = -1.3, p = .20.

**Re-test of emotion recognition abilities**

While both groups showed higher fear recognition scores on re-test, there remained a
highly significant difference between LFS (mean ± SD) 6.9 ± 2.3 and NFS 9.7 ± 0.7,
Mann-Whitney U = 66.5, p < .001. The milder differences in the ability to correctly label
sad and angry expressions also remained, but on this occasion did not reach our corrected
threshold for statistical significance – sadness: LFS 7.6 ± 2.0, NFS 8.4 ± 1.2, U = 159, p
= .09; anger: LFS 8.2 ± 2.2, NFS 9.0 ± 1.0, U = 170.5, p = .15.
Figure 5. Comparing LFS to NFS on the Ekman-Friesen test of facial affect.

A) Distribution of fear recognition scores amongst the 341 male respondents to the on-line Ekman-Friesen test (max score = 10). Those scoring less than or equal to 5 were labelled as ‘low-fear-scorers’ (LFS). Those scoring greater than or equal to 8 were labelled as ‘normal-fear-scorers’ (NFS).

B) Mean number of correct responses for all six ‘basic’ emotions on the Ekman-Friesen test for the 25 LFS and 25 NFS who took part in further study. Scores are out of 10. Error bars indicate ± 1 standard deviation. As well as the difference in fear recognition, LFS were impaired, relative to NFS, at recognition of sad and angry expressions. Sadness: Mann-Whitney $U = 113.5$, $p < 0.05$; anger: Mann-Whitney $U = 84.5$, $p < 0.01$, Bonferroni-Holme corrected.
Mentalising ability

Table 2 shows results for the ToM task. As predicted, LFS made fewer, and less appropriate, mental state attributions to the ToM animations than did NFS. These differences were significant at the 5% level, corrected for multiple comparisons (see table 2). The two groups did not differ in their intentionality ratings of the GD animations. LFS showed a trend towards lower appropriateness scores for these animations but this did not reach significance. There were no differences between the two groups on the length of their descriptions.

Table 2. Scores on the Frith-Happe ToM task  Mean scores (Standard Deviations)

<table>
<thead>
<tr>
<th>Ratings Type (Range) and Group</th>
<th>Animation Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ToM</td>
</tr>
<tr>
<td>Intentionality (0-5)</td>
<td></td>
</tr>
<tr>
<td>LFS</td>
<td>3.7 (0.8)*</td>
</tr>
<tr>
<td>NFS</td>
<td>4.2 (0.5)</td>
</tr>
<tr>
<td>Appropriateness (0-3)</td>
<td></td>
</tr>
<tr>
<td>LFS</td>
<td>1.1 (0.5)*</td>
</tr>
<tr>
<td>NFS</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Length (0-4)</td>
<td></td>
</tr>
<tr>
<td>LFS</td>
<td>3.7 (0.5)</td>
</tr>
<tr>
<td>NFS</td>
<td>3.8 (0.4)</td>
</tr>
</tbody>
</table>

ToM = theory of mind; GD = goal directed

* p < .05, comparing LFS to NFS, corrected for multiple comparisons
Neuroimaging findings

Task Performance

Mean accuracy across both groups was 96% on the gender discrimination task. There were no significant differences between the NFS and LFS subject groups (percent correct ± S.D, NFS: 97 ± 2.5, LFS: 94 ± 4.5, z = -1.7, p = 0.1).

Direct gaze versus averted gaze

Across both subject groups direct, relative to averted, eye-gaze enhanced activity within bilateral amygdala, bilateral FFA and in regions surrounding the anterior STG - areas attributed to the ‘social brain’ (Brothers et al., 1990; see table 3).

I then tested the hypothesis that direct gaze would activate these regions more strongly in NFS compared to LFS. In the comparison of group by condition interaction, (NFS direct gaze – NFS averted gaze) – (LFS direct gaze – LFS averted gaze), I observed greater activity in the left amygdala (x -27, y 0, z -18, z = 3.29), left lateral posterior fusiform gyrus (x -51, y -60, z -12, z = 3.13) and left anterior STG (x -57, y 3, z -3, z = 3.82) in NFS compared to LFS (see figure 6). For each of these regions, there were equivalent activations in the right hemisphere, which showed a trend towards greater activation in NFS compared to LFS (right amygdala, x 30, y -6, z -21, z = 2.40; right posterior FG, x 45, y -69, z -9, z = 1.50; right anterior STG, x 60, y 6, z -3, z = 1.71). Moreover, when a direct gaze - averted gaze contrast was performed separately in both groups, NFS activated left and right amygdala, left anterior STG, left lateral FG, right TP and right
MPFC, whereas LFS showed no activation in voxels within these areas thresholded at \( p < .001 \), uncorrected (see table 3).

Table 3. Regions Activated in a Direct – Averted Gaze Contrast.

<table>
<thead>
<tr>
<th>Group</th>
<th>Brain Region</th>
<th>( x, y, z )</th>
<th>z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>Left amygdala</td>
<td>-21, -3, -21</td>
<td>3.29</td>
</tr>
<tr>
<td></td>
<td>Right amygdala</td>
<td>21, -5, -15</td>
<td>3.24</td>
</tr>
<tr>
<td></td>
<td>Left lateral fusiform gyrus</td>
<td>-54, -63, -12</td>
<td>3.14</td>
</tr>
<tr>
<td></td>
<td>Left lateral fusiform gyrus</td>
<td>-48, -51, -18</td>
<td>3.04</td>
</tr>
<tr>
<td></td>
<td>Right fusiform gyrus</td>
<td>36, -57, -18</td>
<td>2.89*</td>
</tr>
<tr>
<td></td>
<td>Left anterior superior temporal gyrus</td>
<td>-57, 3, -3</td>
<td>3.61</td>
</tr>
<tr>
<td></td>
<td>Left anterior middle temporal gyrus</td>
<td>-60, 0, -18</td>
<td>3.37</td>
</tr>
<tr>
<td>NFS only</td>
<td>Left amygdala</td>
<td>-27, -3, -15</td>
<td>3.30</td>
</tr>
<tr>
<td></td>
<td>Right amygdala</td>
<td>21, -6, -12</td>
<td>3.68</td>
</tr>
<tr>
<td></td>
<td>Left lateral fusiform gyrus</td>
<td>-51, -63, -12</td>
<td>3.60</td>
</tr>
<tr>
<td></td>
<td>Left anterior superior temporal gyrus</td>
<td>-57, 6, -3</td>
<td>3.16</td>
</tr>
<tr>
<td></td>
<td>Left anterior middle temporal gyrus</td>
<td>-48, 0, -18</td>
<td>3.27</td>
</tr>
<tr>
<td></td>
<td>Right temporal pole</td>
<td>39, 21, -36</td>
<td>3.17</td>
</tr>
<tr>
<td></td>
<td>Right medial prefrontal cortex</td>
<td>9, 69, 12</td>
<td>3.04</td>
</tr>
<tr>
<td>LFS only</td>
<td>No significant voxels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FG = fusiform gyrus; STG = superior temporal gyrus; TP = temporal pole; MPFC = medial prefrontal cortex

Activations are significant at \( p < .001 \) (uncorrected), except * \( p = .002 \) (uncorrected).
Figure 6. Neuroimaging results for the interaction (NFS direct gaze – NFS averted gaze) – (LFS direct gaze – LFS averted gaze).

Top: Regions where NFS show greater responses to direct versus averted gaze than LFS. Thresholded at $p < .003$ for display (hence additional activation).

Bottom: Parameter estimates of the activity in the maxima, showing estimates of mean-corrected percent signal change (relative to overall mean activity at each voxel), averaged across repetitions and subjects, for the 2 groups (NFS and LFS) and 2 conditions (direct or averted gaze). Error bars indicate standard errors.
Functional connectivity

I next tested for group differences in the functional connectivity of amygdala responses as a function of the gaze direction of the perceived faces (see Methods). NFS, compared to LFS, showed greater functional coupling of the left amygdala with left anterior STG ($x = -54, y = -3, z = 0, z = 3.56$) and right TP ($x = 36, y = 3, z = -48, z = 3.01$) when processing direct eye-gaze.

Part 1 Discussion

My findings indicate that a significant minority (8%) of the healthy male population (within a university environment) have a marked deficit in the recognition of emotional expressions, especially fear. These deficits are at a level akin to those reported in patients with acquired amygdala damage (Calder et al., 1996). An associated finding is that these impairments extend to encompass other social-cognitive skills. In addition, fear recognition deficits are associated with abnormalities in the brain’s response to socially relevant facial cues as well as in coupling between brain regions previously implicated in processing social information and the development of social skills.

In the Frith-Happé task, LFS attributed fewer and less appropriate mental states to the triangles in the ToM cartoons, but showed no deficits in the attribution of mental states to the GD cartoons. This pattern of scores is remarkably similar to that seen with high functioning autistic / AS subjects as reported by Castelli et al. (2002). Amygdala damaged patients also show deficits on various ToM tasks (Fine et al., 2001; Shaw et al., 2004; Stone et al., 2003), including one requiring anthropomorphizing of abstract animations (Heberlein and Adolphs, 2004). Also, normal subjects show activation in
amygdala, FG, TP and MPfC when attributing social meaning to such abstract animations (Martin and Weisberg, 2003; Schultz et al., 2003). Hence, I show that poor ability to recognise fear from facial expressions amongst members of the general population is predictive of a pattern of social-cognitive deficits consistent with impaired functioning within the so-called social brain (amygdala, FG, STG, TP and MPfC).

It should be noted however, that although I chose a categorical experimental design, comparing very low to normal fear scorers (see methods), these data should not necessarily be interpreted as implying the existence of a ‘special population’ of low-fear scorers. It may indeed prove to be the case that there are genetic and / or other biological variables which can predispose one to poor fear recognition and any associated social-cognitive deficits. However, fear recognition score appears to be a continuous variable (see figure 5a on page 113) and its variation may reflect normal individual differences with multiple and complex aetiologies.

In the neuroimaging experiment, subjects were not required to make explicit judgements about eye-gaze – hence any processing of gaze direction was incidental. I replicated earlier findings suggesting an involvement of the amygdala in processing direct gaze (George et al., 2001; Kawashima et al., 1999; Wicker et al., 2003). Theories of amygdala function stress its role in rapid, and often automatic, detection of biologically (emotionally) significant events (Dolan, 2002). The amygdala acts both to heighten perception of a salient stimulus and enhance memory of its occurrence, thus effecting both immediate and future behaviour (for review, see Dolan, 2002). Amygdala activation to direct eye gaze may serve to increase attention towards the stimulus, thereby enhancing perception of the face and situation. LFS subjects failed to show amygdala activation to direct-gaze, perhaps suggesting they did not register eyes as being salient, an
impairment which may underlie their poor fear recognition ability. Furthermore, as discussed in chapter 1, failure to register socio-emotionally salient stimuli during development could lead to social-cognitive impairment later in life. It is intriguing to speculate that developmental deficits of this sort may have contributed to poor performance of LFS on the Frith-Happé ToM task.

Another area showing greater activation to social stimuli amongst the NFS was found on the left anterior superior temporal gyrus (see figure 3). A number of studies have implicated the STG in processing of seen gaze direction (e.g. Hoffman and Haxby, 2000; Puce et al., 1998), however the locus of activity in these studies was far more posterior to the one reported here, in an area surrounding the temporo-parietal junction (TPJ). The discrepancy between these earlier studies and mine is likely to be due to the focus in the previous studies being on neural correlates of perception of averted gaze direction, rather than the contrast of direct – averted gaze.

Areas corresponding to an anterior STG locus, similar to that activated in my study, were activated in a direct – averted gaze contrast in the study by Calder et al. (2002), albeit in the right hemisphere. I found significant anterior STG activation to direct gaze only in the left hemisphere, although there was a trend towards significance in equivalent areas in the right hemisphere. Interestingly, Wicker et al. (2003) found bilateral activation of the anterior STG, in the same area as my locus, both when subjects had to judge emotion from eyes, keeping gaze constant, and in a direct – averted gaze contrast. An interaction analysis showed that the anterior STG was selectively activated when subjects interpreted emotions that were personally directed.
Wicker et al. (2003) hypothesise that the anterior STG may be a component of a neural system for processing ‘second-person’ intentional relations through eye-contact. Baron-Cohen (1994) has argued that such a system is a precursor to the ‘theory of mind module’. Evidence in favour of this perspective comes from several neuroimaging studies, which show that the anterior STG is one of a number of brain regions associated with the attribution of mental states (see Saxe et al., 2004, for review). Thus, the activation of anterior STG in NFS when someone looks directly at them may reflect engagement of ‘mentalizing networks’, even though the explicit task did not require ToM reasoning. LFS, however, lack this activation, perhaps indicating that they do not automatically analyse the intentions of someone looking directly at them. This may help explain their relatively poor performance on both the fear recognition and the Frith-Happé ToM task in the current study.

In another study of eye gaze processing, Kampe et al. (2003) report activation in the MPfC and the TP in response to direct gaze faces. The authors suggest that activity in these regions, which are associated with theory of mind / mentalization processing (for review, see Gallagher and Frith, 2003), reflects the representation of communicative intent - a process which relies on mentalizing ability (Leslie and Happe, 1989). I observed activation of both these regions in NFS, but not LFS, in response to direct gaze. Moreover, as was seen with the anterior STG, the functional connectivity of the TP with the amygdala was strengthened during direct eye-gaze in NFS but not LFS. The lack of response in these regions demonstrated by the LFS group is consistent with a crucial contribution of MPfC and TP to rapid, automatic engagement of mentalizing.

My functional connectivity analysis suggests links, in NFS, between areas involved in decoding the intentions of the gazer (anterior STG and TP) with those that extract
affective significance from a face (amygdala). Although the direction of the relationship can not be determined, this may be a specific example of the amygdala's neuromodulatory role in enhancing the processing of biologically / socially relevant stimuli in other brain regions (Dolan, 2002). That is to say, when an arousing stimulus (such as someone staring straight at you) signals the need to analyse the intent of a conspecific, the amygdala may promote recruitment of mentalizing regions. If this mechanism is impaired (especially if this happens early in development), deficits in social cognition may arise.

It has been argued that social cognition represents a distinct cognitive ‘domain’ or ‘module’ (e.g. Brothers, 1990). One form of evidence for modularity is the existence of individuals with a selective deficit in the area of cognition under question, especially if this deficit can be associated with a reduction in functional capability in a given neural system (Gardner, 1983). In the domain of social cognition, individuals with autism have been cited as a population with a selective social-cognitive deficit (Brothers, 1990; Karmiloff-Smith et al., 1995) and such individuals fail to activate areas of the ‘social brain’ when processing socially relevant stimuli (for reviews, see Baron-Cohen et al., 2000a; Gallagher and Frith, 2003; Schultz, 2005). Patients with prosopagnosia or lesions to the orbitofrontal cortex provide examples of individuals with selective deficits in subsystems of the social-cognitive ‘module’ resulting from circumscribed brain damage (Brothers, 1990). In the present study I show that subjects from the normal population can demonstrate variability in their social cognitive abilities in the absence of a corresponding variability in global cognitive abilities (there were no differences in IQ between my two groups) and that these deficits are associated with reduced activity and functional connectivity within the ‘social brain’. As such, I provide evidence in support of a social cognitive module, subserving behaviour in response to conspecifics.
**Caveats and further considerations**

The data presented so far beg two important questions. Firstly, what effects, if any, do LFS's social-cognitive deficits have on their day to day lives – are they different from NFS in a more real-world way than captured so far? Secondly, it has recently been suggested that SM's fear recognition deficit may be due to her failure to fixate on the eye region of faces (Adolphs et al., 2005) – is the same true for LFS and, if so, what implication does this have for the conclusions of this study?

Regarding the first question, when I met the LFS subjects they did seem qualitatively different in terms of manner and character than the NFS subjects. Of course, I was not blind to subject group and my observations are likely to have been biased, but LFS did appear to be less likely to engage in spontaneous conversation and to be somewhat more socially withdrawn or anxious than NFS. I hypothesised that, while not being autistic, LFS subjects might show more autistic traits than NFS. To investigate this, the subjects were asked to fill in the autistic-spectrum quotient (AQ) questionnaire (Baron-Cohen et al., 2001b; see Methodology chapter). To test predictions about increased anxiety, particularly social anxiety, amongst the LFS, the trait portion of the Spielberger anxiety inventory (Spielberger, 1983) and the social phobia and anxiety inventory (SPAI; Turner et al., 1999) were administered. Finally, to assess general character, subjects were given the revised NEO personality inventory (NEO PI-R; Costa and McCrae, 1991). Results of these measures are given in part 2 of this chapter.

The question of eye-tracking is potentially very important. In the fMRI experiment, while I presented a fixation cross in the eye region of the stimuli before each block, I did not monitor subjects’ gaze fixation using eye tracking technology. LFS behavioural
performance in the fMRI experiment was high (>94% correct responses) suggesting that their attention was directed towards the stimuli. However, I cannot rule out the possibility that LFS may not have been tracking the eye region of the stimuli as much as NFS, spending more time on other facial features such as the mouth. If this is the case, it may account for the low fear scores of the LFS group as well as their failure to activate the amygdala and other areas in response to direct gaze. This could have profound implications for any conclusions drawn about the aetiology of the social cognitive deficits seen in LFS. Therefore, I asked a group of LFS and NFS to participate in the eye-tracking experiment, outlined in chapter 2. Results are given in the next section.

**Part 2 – LFS are more anxious than NFS and spend less time fixating eyes**

**Personality and anxiety questionnaires**

The AQ, NEO PI-R, trait anxiety and SPAI questionnaires were administered, following the protocol explained in chapter 2 (methods).

<table>
<thead>
<tr>
<th></th>
<th>LFS</th>
<th>NFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.5</td>
<td>33.1</td>
</tr>
<tr>
<td>IQ</td>
<td>115.7</td>
<td>119.9</td>
</tr>
<tr>
<td>N</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>SD</td>
<td>10.88</td>
<td>8.31</td>
</tr>
<tr>
<td>Average Fear Score</td>
<td>5.9</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>1.48</td>
<td>.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Average fear score is the mean from the original online test and the in-laboratory re-test
were available to take part; their characteristics are given in table 4. Average fear score remained significantly lower in this truncated sample – $U < .001, p < .001$. Neither age – $t(30) = .71, p > .4$ - nor IQ were significantly different – $t(30) = -1.32, p = .20$.

**Autistic-spectrum quotient (AQ)**

AQ results are given in table 5. Although LFS reported experiencing a slightly greater number of autistic-traits than NFS, this difference was not significant $t(48) = 0.97, p = .34$.

I compared the AQ scores of the LFS and NFS groups to the norm data published by Baron-Cohen et al. (2001b). These authors report a mean AQ score of 17.8 ($SD = 6.8$) for a random sample of 76 males recruited by mail-out to addresses in East-Anglia (mean age 37, $SD = 7.7$) and 18.6 ($SD = 6.6$) for a sample of 454 male university students (mean age 21 years, $SD = 2.9$). NFS had a significantly lower score than the sample of male university students – $t(477) = 2.33, p < .05$, Bonferroni-Holm corrected) but not the random sample of East Anglican males – $t(477) = 1.56, p > .2$, corrected) LFS were not significantly different from either group (both $p > .5$, corrected).
For a sample of 58 individuals with AS or high-functioning autism, Baron-Cohen et al. (2001b) report a mean AQ score of 35.8 (SD = 6.5). Both LFS and NFS AQ scores were significantly lower than that of this ASD sample (LFS: \( t(81) = 11.8, p < .001 \), NFS: \( t(81) = 13.3, p < .001 \), Bonferroni-Holm corrected).

**NEO Personality Inventory (NEO PI-R)**

Figure 7 presents the personality characteristics of the LFS and NFS groups, measured on Costa and McCrae's (1991) 'five factors' of personality. These scores were entered into a MANOVA, with group (LFS or HFS) as a dependent variable. There was a significant effect of group – Pillai's trace = .521, \( F(5,24) = 5.2, p = .002 \) – indicating that LFS and NFS differed in terms of overall personality. ANOVAs were then carried out on each personality factor separately. The groups differed significantly in terms of neuroticism – \( F(1,28) = 6.3, p = .018 \) – and openness to experience – \( F(1,28) = 16.1, p < .001 \). There were no other significant effects (all \( p > .12 \)).
One sample t-tests were conducted for each group separately to compare their scores on the five personality factors to the average for the normal population, as reported by Costa and McCrae (1991). Only two results remained significant following correction for multiple comparisons: LFS were significantly more neurotic \(- t(14) = -3.9, p = .02\) corrected - and NFS were significantly more open to experience \(- t(16) = 7.4, p < .01\), corrected - than the general population.

The NEO PI-R breaks each personality factor down into six ‘facets’, or sub-scales, allowing a more fine-grained analysis of character. Figure 8 compares LFS and NFS on the sub-scales of ‘neuroticism’ and ‘openness to experience’. Because of the high number of comparisons, the results were corrected for multiple comparisons using the Bonferroni correction.
of comparisons involved and the relatively small sample sizes, statistical analyses are not offered for these data.

**Anxiety measures**

Table 6 gives the results of the Spielberger trait anxiety questionnaire and the social phobia and anxiety inventory for LFS and NFS subject groups. These data were entered into a MANOVA, with Marlowe-Crowne social desirability scale (see chapter 2) as a co-variate.

The two groups differed significantly overall – Pillai’s trace = 0.53, $F(3,26) = 9.8, p < .001$. Two ANOVAs were then conducted with each scale separately (again with Marlowe-Crowne score as a co-variate). There was a significant effect of group (LFS/NFS) on both measures – trait anxiety: $F(1,28) = 8.6, p = .007$; social phobia scale: $F(1,28) = 5.4, p = .03$.

<table>
<thead>
<tr>
<th></th>
<th>Trait Anxiety</th>
<th>Social Phobia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T scores</td>
<td>Scale</td>
</tr>
<tr>
<td>LFS</td>
<td>60</td>
<td>73</td>
</tr>
<tr>
<td>SD</td>
<td>9.2</td>
<td>21.6</td>
</tr>
<tr>
<td>NFS</td>
<td>52</td>
<td>58</td>
</tr>
<tr>
<td>SD</td>
<td>6.1</td>
<td>14.7</td>
</tr>
</tbody>
</table>

*Population norms:* For trait anxiety, the average score for the population is 50 (Spielberger, 1983). For the SPAI, a group of 34 definitely non-socially anxious university students scored 49 for the social phobia scale, whereas a group of 51 socially-phobic university students scored 99 (Turner et al., 1999).
Figure 8. LFS and NFS compared on the sub-scales of the neuroticism and openness to experience personality factors. Results are given in T scores, where 45 – 55 is the average range.
Eye-tracking experiment

This experiment was conducted more than two years after the original LFS/NFS project began. Therefore, it was only possible for ten of the original sample to take part (4 LFS and 6 NFS). To make a reasonable sample size, a number of female LFS and NFS, identified from the original online data, were recruited. However, the quality of the eye-tracking recording was too poor to be used in several cases. The final sample consisted of 6 LFS (3 male) and 13 NFS (10 male). Group characteristics are given in table 7.

The gaze fixation data were entered into an ANOVA with group as a between-measures variable and phase and emotion as repeated-measures variables. The independent variable was the percentage of fixations made to the eyes. IQ was included as a co-variate. There was no significant effect of phase or significant interactions between phase and the other variables (all $F < 1.8$, all $p > .2$); therefore, for display purposes, data from both phases are combined. Figure 9 displays the percentage of fixations made to the eyes, broken down by emotion and group. Even with the small sample size, the effects group, $F(1,13) = 5.6$, $p = .03$, and emotion, $F(5,65) = 2.6$, $p = .03$, were both significant. There were no significant interactions (all $p > .1$).

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>IQ</th>
<th>Average Fear</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LFS</strong></td>
<td>Mean</td>
<td>35.5</td>
<td>118.8</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>15.52</td>
<td>8.80</td>
</tr>
<tr>
<td><strong>NFS</strong></td>
<td>Mean</td>
<td>32.1</td>
<td>122.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>12.14</td>
<td>9.53</td>
</tr>
</tbody>
</table>

Average fear score is the mean from the original online test and the in-laboratory re-test.
Figure 9. LFS subjects fixate on the eyes less than NFS subjects.
Error bars indicate ± 1 standard error.

Post-hoc comparisons were used to investigate the main effect of emotion. These revealed that subjects spent significantly less time fixating the eyes when viewing disgusted faces compared to all other emotions (all $p < .05$, Bonferroni corrected). In addition, subjects spent significantly less time viewing angry compared to surprised faces ($p < .05$, Bonferroni corrected). No other pairwise comparisons were significant following correction for multiple comparisons.

Within the LFS and NFS groups, there were no significant correlations between the percentage of eye fixations made, the anxiety measures and fear recognition ability (all $p > .1$).
Table 8 gives the results of the relevant personality and anxiety measures for the new sample. The pattern of findings is very similar to the original sample; the exception being that neuroticism is this time slightly higher in the NFS group. However, probably due to the small sample size, none of these differences this time reach significance (all p > .1).

### Table 8. Personality and anxiety measures for the LFS and NFS samples who took part in the eye-tracking experiment.

<table>
<thead>
<tr>
<th></th>
<th>Neuroticism</th>
<th>Openness to Experience</th>
<th>Trait anxiety T score</th>
<th>Social Phobia Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LFS</strong></td>
<td>Mean 56</td>
<td>61</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>SD 13.5</td>
<td>6.6</td>
<td>6.4</td>
<td>18.9</td>
</tr>
<tr>
<td><strong>NFS</strong></td>
<td>Mean 58</td>
<td>63</td>
<td>56</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>SD 12.9</td>
<td>7.2</td>
<td>8.8</td>
<td>33.8</td>
</tr>
</tbody>
</table>

**Part 2 Discussion**

I found no evidence to support my prediction that LFS would experience more autistic traits than NFS. In addition, the mean number of autistic-traits reported by LFS is very similar to that of the norm data published by Baron-Cohen et al. (2001b). It is therefore very unlikely that poor fear recognition ability is associated with a greater incidence of ASD-like behaviour\(^1\).

On the other hand, there is some evidence that NFS demonstrate fewer autistic-traits than the average male – their scores were significantly lower than the university student

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\(^1\) A caveat is that this was a self-report measure and therefore LFS may be under-reporting their autistic-like symptoms (perhaps because of lack of insight). However, individuals with a diagnosed ASD do not seem to have this problem (they rate themselves highly on the AQ – see Baron-Cohen et al, 2001). An objective measure of autistic symptoms might be beneficial, but it is difficult to think of one that would be sensitive enough to pick up the subtle differences that are likely to exist between LFS and NFS – although the ADOS is a possibility.
sample reported by Baron-Cohen et al. (2001b). However, when NFS were compared to the random sample of East-Anglican men the difference was not significant (although it was in the required direction). It is difficult to know which group is the best comparison for the NFS sample – in age they more closely resemble the random sample, but in other characteristics they probably more closely match the university students (the NFS sample is made up mostly of undergraduate and post-graduate students and some faculty staff). Therefore, it is possible that better than average fear recognition is associated with better than average social functioning. Comparison of NFS with a well-matched group is clearly required to confirm or disconfirm this finding.

On the other measures of personality and anxiety, there were clear differences between the two groups. LFS rated themselves as being more neurotic than NFS. Examination of the neuroticism sub-scales suggests that this difference is driven largely by an increased tendency for LFS to feel anxious, depressed and self-conscious (on the NEO PI-R, self-consciousness is “akin to shyness and social anxiety”, see Costa and McCrae, 1991, pg. 16). The other measures confirmed this finding – LFS show greater general (trait) and social anxiety than NFS.12

Anxiety, particularly social anxiety, might be a product of poor social cognitive ability. For example if an individual has difficulty understanding social signals he might experience adverse peer interactions, which could lead to rejection and anxiety (Ginsburg

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12 It is important to note that, while significantly more anxious than NFS, LFS should be thought of as being towards the top of the normal range rather than abnormally (clinically) anxious. For example, for trait anxiety the mean LFS score corresponds to the 82nd percentile on the published norm data; for neuroticism it is the 87th percentile (NFS scores corresponded to the 60th percentile on both measures, unfortunately detailed normed data is unavailable for the social phobia scale).
et al., 1998). Alternatively, or in addition, anxiety may contribute to poor social cognitive ability. For example, if social stimuli cause over-arousal they might be actively avoided, with the result that subtle, but vital, social cues are missed. Over time, this could result in under-development of neural systems which normally subserve social behaviour. A similar idea is found in the hyper-active amygdala model of ASD (see chapter 1 and Dalton et al., 2005; Nacewicz et al., in press). Suggestions for experiments to investigate this possibility are given in the next section.

Inconsistent with my finding of a relationship between anxiety and poor fear recognition is the established literature associating high anxiety with hyper-vigilance of potentially threatening stimuli, of which fearful faces are considered to be one (for review see Dalgleish and Power, 1999). For example, anxious individuals have an attentional bias for fearful faces (Fox et al., 2005; Georgiou et al., 2005) and both high trait (general) anxiety (Surcinelli et al., 2006) and high social anxiety (Richards et al., 2002) individuals show an advantage for recognising fear in facial expressions. An explanation for this discrepancy might relate to the different strategies that people employ to cope with anxiety. While the majority of individuals appear to react to anxiety with hyper-vigilance (Dalgleish and Power, 1999), there is evidence that others react with sensory defensiveness, avoiding any arousing stimuli (Pfeiffer et al., 2005). Again, more experiments will be required to investigate this further.

NFS rated themselves as more open to experience than LFS. This was not because LFS scored low on openness (they were in the normal range) but, rather, because NFS scored significantly above the normal range. Two recent, large scale studies are consistent with this finding, showing that openness to experience correlates with the ability to recognise emotions presented in multiple domains, including from facial expressions (Matsumoto et
al., 2000; Terracciano et al., 2003). Open individuals tend to be intellectually curious, imaginative, and sensitive to aesthetics and inner feelings (Costa and McCrae, 1991). Thus, they are particularly attentive and receptive to their environment and the world around them, which may explain their heightened ability to read the emotions of others.

LFS spent less time fixating the eye regions of faces than controls, which, like SM, might contribute to their poor fear recognition ability. This finding may have profound implications for interpretation of the fMRI results presented in part 1 of this chapter. It is impossible to be certain about the fixation behaviour of our original sample – only a few took part in the later eye-tracking study and no eye-tracking was performed during the neuroimaging experiment itself. Still it seems a distinct possibility that, during the fMRI experiment, LFS were fixating the eye region less than controls. If this is the case, then the reduced brain activity in LFS could simply reflect the fact that they were not engaging the most emotive parts of the stimuli (the eyes) as much as NFS. What this means in terms of understanding the social-cognitive deficit in LFS is discussed in the next section.

**Summary, caveats and future directions**

In part 1, I showed that poor fear recognition is associated with poor theory of mind ability and with reduced activation of diffuse areas of the social brain. In part 2, I found that poor fear recognition is also associated with increased levels of anxiety and with reduced time spent fixating the eyes in faces. The eyetracking results question the interpretation of the neuroimaging findings: were the brains of the LFS and NFS participants reacting differently to the same visual input or were the subjects behaving differently and therefore receiving different visual input? More experiments are required to answer this question and some suggestions are given below. Given the research
showing the crucial role of the eyes in recognising fearful expressions (Adolphs et al., 2005; Kohler et al., 2004; Smith et al., 2005), the eyetracking results presented here suggest that LFS are poor at recognising fearful faces because they spend less time fixating the eyes. The data collected so far are merely correlational; therefore it will require more work to positively prove this assertion – again, some ideas for appropriate experiments are given below. The most important unsolved question is why LFS do not look at eyes as much as NFS and how this might relate to their higher levels of anxiety, their abnormal neural response to direct gaze and their impaired ToM abilities. At least four possibilities exist:

1) LFS do not register eyes as salient and so are not drawn towards them. Parallels may be drawn here to the hypoactive amygdala model of ASD (see chapter 1 and Schultz, 2005), where it is proposed that the amygdala fails to flag certain social stimuli, such as eyes, as important, with the result that attention is not directed towards them.

2) LFS find eyes aversive (over-arousing) and so actively avoid them. This echoes the hyper-active amygdala model of ASD (see chapter 1 and Dalton et al., 2005; Nacewicz et al., in press); which suggests that it is hyper-activity of the amygdala which leads to emotional stimuli being avoided. The fact that LFS are more anxious, including socially anxious, than NFS, could be considered to be consistent with this account.

3) A neurological reason not related to detecting emotional salience and/or the amygdala. For example, Wong et al. (2005) suggest that reduced fixation to the upper part of the face and declining ability to recognise fear and anger in old age might be related to front lobe atrophy affecting the integrity of the frontal eye fields. It may be beneficial to investigate the integrity of these circuits in LFS.
4) A behavioural reason not related to emotional salience or anxiety. Aberrant visual scanning of faces by LFS may be due to an unusual cognitive strategy employed when attempting to gain information from faces. One could postulate a number of possible causes for this; untreated eyesight problems in childhood, for instance.

There are numerous experiments which could be conducted to take these findings forward. Probably the most crucial would involve measuring the neural responses of LFS and NFS to socially salient stimuli (e.g. faces with direct gaze) while manipulating where on the stimulus they are fixating (e.g. either the eyes or the mouth). Gaze fixation patterns should be carefully monitored using an eyetracker and autonomic responses, such as SCRs, should be recorded. Firstly, this experiment would show whether LFS brains do indeed react differently to the same visual input of a socially salient stimulus or whether the fMRI findings presented in part 1 of this chapter can be explained purely by differences in the way LFS viewed the faces. Secondly, it would test (1) and (2) above. If eyes are less salient to LFS, one would predict that LFS subjects would show reduced autonomic or amygdala activity to eyes (versus mouths) compared to NFS. On the other hand, if eyes are hyper-arousing to LFS, heightened responses would be expected. Finally, if no differences in autonomic and/or amygdala activity can be observed between LFS and NFS when they are made to look at the eyes, then this would count against both (1) and (2) and one could focus attention on alternative explanations for the failure to fixate eyes in LFS – e.g. (3) and (4).

Testing if a failure to look at eyes actually causes poor fear recognition in LFS may be difficult, but one possibility is to borrow an experiment from Adolphs et al.'s (2005) study of SM. While SM does not spontaneously look at the eyes she is able to do so when instructed, with the result of a dramatic improvement in her fear recognition. When the
task is repeated a few weeks later, however, both the failure to fixate the eyes and the poor fear score have returned. Together, these results suggest that poor eye fixation is the mechanism for poor fear recognition in SM. A similar experiment with LFS would provide useful data for interpreting the cause of their fear recognition deficit.

Finally, it would be useful to examine the cognitive strategies used by LFS when they attempt to classify fearful expressions. Probably the most precise way to do this would be to use the Bubbles task (Gosselin and Schyns, 2001). This would give exact details about the features of the face that are being used by LFS when they attempt to identify a given expression.

As stated earlier, part 2 of this chapter was completed towards the end of the time available for this PhD and considerably after part 1 was began. Unfortunately, therefore, there is neither the time nor the necessary numbers of LFS participants to conduct the experiments described above. Instead, the remaining chapters of this thesis focus on fear recognition and eyetracking in AS, with a view to testing predictions made by the hyper- and hypo-active amygdala models of ASD.
Chapter 4 – Fear recognition in Asperger’s syndrome

Introduction and Summary

In part 1 of this chapter I examine the controversial question of whether people with an ASD are impaired at recognising fear from facial expressions, as well as the other negative emotions, in line with an amygdala involvement in the condition. I show that a group of high-functioning Asperger’s syndrome (AS) subjects are indeed impaired at recognising fear and also sadness relative to age, IQ and gender matched controls. However, there is great variability in the AS group: their ability to recognise fear ranges from above average to severely impaired, which may help explain the equivocal findings in the literature regarding this issue. In part 2, I investigate the origin of the fear recognition deficit in AS and the reasons behind its variable manifestation. I show that poor fear recognition amongst AS subjects is associated with a failure to fixate the eye region of faces. This pattern is reminiscent of patient SM and is discussed in terms of current models of amygdala pathology in ASD (the hyper- and hypo-responsive models). In the next chapter I test predictions from these competing models, thereby investigating the underlying cause of the reduced eye fixation and poor fear recognition ability in some AS subjects.

Part 1 – Recognition of facial affect in AS

Methods

Twenty-one individuals with a diagnosis of AS took part in this study (see chapter 2 for details of recruitment and diagnosis) along with twenty-one controls, matched as closely
as possible for gender and age. Table 9 gives the age, gender, IQ and ADOS characteristics for these groups.

Table 9. Group characteristics for 'recognition of facial affect in AS' study.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Gender</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
<th>Full IQ</th>
<th>DTVP Score</th>
<th>AQ</th>
<th>ADOS Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS Mean (SD)</td>
<td>33.8 (13.60)</td>
<td>16 M</td>
<td>115.8 (9.68)</td>
<td>116.2 (13.73)</td>
<td>117.9 (11.67)</td>
<td>106.7 (6.66)</td>
<td>37.1 (6.21)</td>
<td>11 Autism</td>
</tr>
<tr>
<td>Controls Mean (SD)</td>
<td>32.1 (11.58)</td>
<td>16 M</td>
<td>115.1 (8.19)</td>
<td>115.5 (8.75)</td>
<td>117.2 (8.00)</td>
<td>106.3 (6.16)</td>
<td>14.9 (8.58)</td>
<td>NA</td>
</tr>
</tbody>
</table>

DTVP = Developmental Test of Visual Perception. ADOS = autism diagnostic observation schedule. AQ = Autistic-spectrum quotient.

In (Baron-Cohen et al., 2001b), the mean AQ score for the AS sample was 35.8 (SD = 6.5); the mean score for a large sample of normal controls was 16.4 (SD = 6.3).

There were no significant differences between any of these variables (all \( p > .72 \)) apart from AQ (\( p < .001 \)).

Subjects completed our computerised version of the Ekman-Friesen test of facial affect recognition (see chapter 2 for further details) in the laboratory. The six emotion labels were presented adjacent to each image and subjects indicated their responses via a mouse click. There was an unlimited time to answer.

**Results**

Figure 10 summarises the Ekman-Friesen test results as a box-plot. As in chapter 3, the data were not normally distributed and could not be normalised by transformation; therefore Mann-Whitney tests are used to compare group differences. AS subjects performed significantly worse than controls at recognising fearful (\( U = 124, \ p < .05, \) Bonferroni-Holm corrected) and sad (\( U = 104.5, \ p < .05, \) corrected) facial expressions.

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Figure 10. Results of the Ekman-Friesen test of facial affect recognition for AS subjects and age and gender matched controls. Boxes show the median (black line) and the inter-quartile range (IQR, edges of boxes). Whiskers are 1.5 * IQR. Circles represent mild outliers (between 1.5 and 3 * IQR) and stars represent extreme outliers (> 3 * IQR).

Of note is the generally higher degree of variability amongst the AS subjects (see figure 10), which is particularly evident for fearful expressions: many individuals are performing normally (the mode fear recognition score is 10/10 for both groups) but a number are severely impaired. Conover’s squared ranks test\(^1\) (Conover, 1999) confirms that the variability in fear recognition scores is higher within the AS group (SD = 2.93 for AS, 1.34 for controls, \(p = .01\)). There is also a significant difference in variance for angry expressions (SD = 2.10 for Asperger’s, 1.23 for controls, \(p = .02\)) but not for any other emotion.

\(^1\) This is a non-parametric test for equality of variance between two sample populations. Levene’s test or the F ratio test would be inappropriate in this case as both assume that the data come from a normally distributed population.
Reaction times\textsuperscript{14} were slightly slower for the AS group, although this was not significant (mean ± SD, Asperger's, 1061 ± 542 msec; controls, 909 ± 363 msec; \(t(40) = 1.05, p = .3\)), suggesting that the differences between the two groups were not due to a speed-accuracy trade-off. In addition, there were no significant correlations between fear or sadness recognition score and reaction time, age, verbal IQ, performance IQ or DTVP score for either group (all \(r < .28\), all \(p > .21\)), suggesting that differences in cognitive ability could not explain the variability in fear and sadness recognition ability.

In the AS group, neither fear or sadness recognition significantly correlated with the severity of autistic symptomology, measured either as part of the ADOS or self-reported by the AQ (table 10).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
 & ADOS Com & ADOS RSI & ADOS Total & AQ \\
\hline
Fear recognition score \(r\) & .01 & -.05 & -.01 & .25 \\
Sad recognition score \(r\) & -.24 & .03 & -.07 & .05 \\
\hline
\end{tabular}
\caption{Spearman's correlations between fear and sadness recognition scores and measures of autistic impairment. All \(p > .31\). ADOS = autism diagnostic observation schedule AQ = autistic-spectrum quotient}
\end{table}

To further investigate the fear and sadness recognition deficits in the AS group, I characterised the errors that both groups made when misidentifying these emotions. For fearful faces, the groups made similar patterns of errors, usually misidentifying fearful faces as either surprised or disgusted (see table 11). Misidentifying fear as anger was the third most common error, seen more often in the AS group. However, Mann-Whitney

\textsuperscript{14}These are the mean reaction times, averaged over all emotions. Unfortunately, due to loss of the raw data it was not possible to present reaction times for the individual emotions. However, the Ekman-Friesen test is repeated in part 2 of this chapter, where on this occasion the reaction time data are given in full.
tests for each emotion revealed no significant differences between the two groups’ error patterns, even before correction for multiple comparisons (all $p > .36$, uncorrected).

<table>
<thead>
<tr>
<th></th>
<th>Surprised</th>
<th>Angry</th>
<th>Disgusted</th>
<th>Sad</th>
<th>Happy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AS</strong></td>
<td>Mean % of errors</td>
<td>56.5</td>
<td>16.1</td>
<td>26.7</td>
<td>.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>40.04</td>
<td>30.20</td>
<td>33.68</td>
<td>.00</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td>Mean % of errors</td>
<td>60.6</td>
<td>7.6</td>
<td>31.8</td>
<td>.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>49.03</td>
<td>17.26</td>
<td>41.13</td>
<td>.00</td>
</tr>
</tbody>
</table>

Table 11. Pattern of errors made when misidentifying a fearful face, split by group. The percentage of times that each emotion was chosen in place of fear (the correct answer) was calculated separately for each subject and the mean of these data is shown above. Subjects who made no errors were not included in the analysis.

For the AS group alone, I then investigated whether the pattern of errors varied with fear recognition score by splitting the group into three sub-groups: those who scored $\leq 5$ for fear recognition, those who scored 6 or 7 and those who score 8 or 9 (see table 12). The data suggest that progressively more fearful faces are misidentified as angry as fear score drops. However, a Kruskal-Wallis test showed that this was not significant ($\chi^2 = 3.1, p = .24$), perhaps largely because of the small sample size (see table 12).
Table 12. Pattern of errors when AS subjects misidentify a fearful face, split by fear recognition score.

Table 13 shows the pattern of errors when subjects misidentified a sad face. Again, the pattern of errors was similar for each group, except that AS subjects sometimes identified a sad face as surprised or happy, which controls never did. However, there were no significant differences between the two groups after correction for multiple comparisons (all \( p > .24 \)) – although for surprised the difference was significant before correction (\( p = .047 \)). No clear patterns emerged when splitting the AS group by sadness score and, therefore, these data are not shown on this occasion.

Table 13. Pattern of errors made when misidentifying a sad face, split by group. The percentage of times that each emotion was chosen in the place of sadness (the correct answer) was calculated separately for each subject; the mean of these data is shown above. Subjects who made no errors were not included in the analysis.
Discussion

As predicted, individuals with AS were impaired at recognising fearful faces compared with age and gender matched controls. Like patients with amygdala damage, this extended to other negative emotions – there was a significant effect for sad faces and a trend towards an effect for angry faces. These data replicate studies by Howard et al. (2000) and Pelphrey et al. (2002), who both found a fear recognition impairment in adults with high functioning autism or AS, as well as trends toward an impairment for recognising sad and angry expressions. However, the present findings do not concur with studies by Adolphs et al. (2001), Grossman et al. (2000) or Castelli (2005), who all failed to find an impaired ability to recognise fear or any of the other ‘basic’ emotions in ASD.

As discussed in chapter 1, the latter two of these studies were conducted with children (mean chronological age 11.8 and 12.3 respectively, verbal age 9.3 years for the second study) rather than adults, which may go some way to explaining the negative findings. For example, control children may not yet be developed enough to complete the task successfully, which would appear to be the case in the Grossman et al. (2000) study where control children only correctly identified 50% of the fearful faces (Asperger’s children identified 48% correctly). The other study which failed to find a fear recognition deficit in ASD was conducted with adults (Adolphs et al., 2001). However, as discussed in chapter 1, this was with a small sample size (7 ASD subjects) and examination of the data shows that all but one ASD subject scored below the control mean (see figure 2 of Adolphs et al., 2000), suggesting the possibility of a type II error.

A striking feature of the data reported here is the high degree of variability amongst the AS group, whose fear recognition scores showed over twice the standard deviation of the control sample. No previous studies have highlighted such a difference, although the data
reported by Pelphrey et al. (2001) shows an effect of similar magnitude (2x that of controls). Howard et al. (2000) and Grossman et al. (2000) report milder differences in the same direction (SD of AS group 1.2x and 1.4x that of controls respectively), while Castelli et al. (2005) find the opposite effect, albeit using a different paradigm (Asperger’s 0.9x controls). Adolphs et al. (2001) do not provide the information, but they do note that two of their AS subjects performed noticeably worse than the rest of the group. There could be many reasons for this variability. Individuals with an ASD are a notoriously heterogeneous group and the manifestation of clinical symptoms can be quite variable (Wing and Gould, 1979). Whether this reflects significant differences in underlying pathophysiology or whether it is due to overlying, modulatory mechanisms is a pertinent question both to the study of the condition as a whole and to the current data. Variable fear recognition ability in ASD may indicate the existence of pathophysiologically distinct sub-groups or it may mean that some have developed compensatory cognitive strategies while some have not. This question will be returned to in later chapters. Whatever its cause, if there is greater variability in fear recognition amongst those with an ASD, it may go a long way to explaining the inconsistency in research findings, especially given the typical sample sizes of ~20 subjects.

When they misidentified a fearful face, the AS group made similar errors to the control subjects, usually mistaking it for a surprised face. The similarity between the two expressions was noted by Darwin (1872/1998) and this pattern of errors concurs with those found in previous studies (Ekman and Friesen, 1976; Young et al., 1997). However, AS subjects who had a low fear score often misidentified fear as anger – a mistake which is uncommon amongst my controls as well as those of other studies (Ekman and Friesen, 1976; Young et al., 1997). These differences did not reach statistical significance but they may be worth pursuing in the future, as they perhaps suggest that the AS subjects who are
poor at recognising fear do not simply have an altered threshold when it comes to differentiating fear and surprise but have a more profound problem with emotion recognition. A similar situation is evident for sad expressions, the other emotion for which AS subjects were also significantly worse at recognising than controls. Again, the general pattern of errors (misidentifying sad expressions as fearful or disgusted) was similar between the two groups and concurred with previous studies (Ekman and Friesen, 1976; Young et al., 1997). However, the AS group did not simply make more of the usual errors - 10% of their mistakes were caused by misidentifying sadness as surprise, something that controls never did. Clearly data on more subjects is required before definitive conclusions can be drawn, but this type of error analysis could prove useful in characterising the emotion recognition deficits in ASD.

The two groups were well matched in terms of age, IQ and basic visual perceptual abilities (as measured by the DTVP). In addition, reaction times did not differ significantly between the groups and none of the variables just mentioned correlated with fear or sadness recognition ability within the AS group. Therefore, neither differences in cognitive/perceptual abilities or in a speed-accuracy tradeoff can be invoked to explain the observed fear and sadness deficits. Rather, they would appear to reflect a specific impairment in social-perceptual ability and therefore support the existence of a distinct social-cognitive ‘module’, removed from other areas of cognition.

Neither fear or sadness recognition impairment correlated with the severity of autistic symptomology as measured by the ADOS or AQ, perhaps indicating that deficits in social-perception can not predict deficits in day to day social interaction and communication. There may be a number of reasons for this: some practical, to do with problems concerning measurement and operationalisation of psychological concepts, and
others more theoretical, concerning the place of social-perceptual deficits in the autism phenotype. These issues will be discussed in more detail in the discussion to chapter 5 and, particularly, in the general discussion in chapter 7, where it will be possible to place them in the context of the other findings in this thesis.

Taking the evidence as a whole, my data adds to a growing consensus of a fear recognition deficit in adults with high functioning autism or AS. However, the reasons and causes of this are yet to be explored. As discussed in chapter 1, a number of studies have shown that those with an ASD fail to fixate the eyes in faces as much as controls (Dalton et al., 2005; Klin et al., 2002; Pelphrey et al., 2002). Given the association between the eyes and fear recognition in normal individuals (chapter 3 and Smith et al., 2005) and SM (Adolphs et al., 2005), linking the two in ASD seems an obvious step, yet to date no studies have tried to do this formally. The next section attempts such an inquiry.

**Part 2 – Poor fear recognition in AS is associated with a failure to fixate eyes**

**Methods**

18 of the AS subjects who participated in part 1 provided data for this stage of the study. Of those whose data is missing, one was unable to take part due a lack of wheelchair access to the testing room, one became anxious during the testing procedure and asked to stop and one completed the task but his recording was not of sufficient quality to be used. The AS group were matched in terms of age and gender with 18 control subjects, who had also participated in part 1. Unfortunately, eyetracking data was corrupted for one control subject, leaving 17 participants. The AS subjects' impairment in recognising
fearful and sad facial expressions persisted with these truncated groups – fear, \( U = 95, p = .025; \) sad, \( U = 73.5, p = .003 \). Table 14 displays the group characteristics.

The subjects took part in the eyetracking task as described in chapter 2. To recap, subjects had their eye movements recorded during two experimental phases. In phase 1 there was no task; subjects were told to, “look at the faces however they wanted to”. In phase 2, after viewing each photograph, subjects were required to choose which emotion they thought the person was expressing from a list of the six basic emotions. Therefore, as well as having their eye movements recorded, subjects also repeated the Ekman-Friesen test of facial affect. In terms of the eyetracking data, the dependent variables were the amount of time spent fixating the eye and mouth region, expressed as a percentage of the total number of fixations to the face.

**Table 14.** Group characteristics for the subjects who took part in the eye-tracking study.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Gender</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
<th>Full IQ</th>
<th>DTVP Score</th>
<th>AQ score</th>
<th>ADOS Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AS</strong> (Mean (SD))</td>
<td>33.2 (13.97)</td>
<td>15 M</td>
<td>116.8 (10.08)</td>
<td>120.0 (15.10)</td>
<td>120.7 (12.76)</td>
<td>106.3 (6.67)</td>
<td>36.6 (8.26)</td>
<td>8 Autism</td>
</tr>
<tr>
<td></td>
<td>3 F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 Autistic spectrum</td>
</tr>
<tr>
<td><strong>Controls</strong> (Mean (SD))</td>
<td>31.9 (11.58)</td>
<td>14 M</td>
<td>115.1 (8.37)</td>
<td>115.9 (8.87)</td>
<td>117.4 (8.26)</td>
<td>106.7 (6.14)</td>
<td>14.6 (9.17)</td>
<td>NA</td>
</tr>
</tbody>
</table>

DTVP = Developmental Test of Visual Perception. ADOS = autism diagnostic observation schedule. AQ = Autistic-spectrum quotient

In (Baron-Cohen et al., 2001b), the mean AQ score for the AS sample was 35.8 (SD = 6.5); the mean score for a large sample of normal controls was 16.4 (SD = 6.3).

There were no significant differences between any of these variables (all \( p > .38 \)), apart from AQ (\( p < .001 \)).
Results

Emotion recognition re-test

Table 15 shows the results of the Ekman-Friesen emotion recognition test, which subjects repeated as part of phase 2 of the eyetracking experiment. Both groups showed an improvement on the first time they took the test, but the rank order of results did not change, as shown by non-significant Wilcoxon signed ranks tests for each emotion (all $p > .35$).

<table>
<thead>
<tr>
<th>Emotion</th>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Happy</td>
<td>AS</td>
<td>9.9</td>
<td>.24</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>10.0</td>
<td>.00</td>
</tr>
<tr>
<td>Sad</td>
<td>AS</td>
<td>7.7</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>8.2</td>
<td>1.25</td>
</tr>
<tr>
<td>Fearful</td>
<td>AS</td>
<td>7.5</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>8.8</td>
<td>1.33</td>
</tr>
<tr>
<td>Angry</td>
<td>AS</td>
<td>8.5</td>
<td>1.34</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>8.7</td>
<td>1.10</td>
</tr>
<tr>
<td>Surprised</td>
<td>AS</td>
<td>8.5</td>
<td>2.20</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>8.8</td>
<td>1.29</td>
</tr>
<tr>
<td>Disgusted</td>
<td>AS</td>
<td>6.6</td>
<td>2.57</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>8.1</td>
<td>2.26</td>
</tr>
</tbody>
</table>

Table 15. Re-test of the Ekman-Friesen test with the AS group and controls.

AS subjects were again significantly impaired at recognising fearful faces ($U = 85, p < .05$, corrected), but there were no significant effects for the other emotions after correcting for multiple comparisons (all $p > .2$ corrected).

Variability in responses was again generally higher for the AS group, although to a much smaller degree than for the first test, especially for fearful expressions. This was reflected in the results of Conover’s squared ranks test for equality of variance, which were non-significant for each emotion following correction for multiple comparisons (all $p > .6$; although the variability for surprise was significantly greater in the AS group before correction – $p < .025$).
The reaction times for the emotion recognition task are shown in figure 11, split by emotion and group. These data were entered into an ANOVA. There was a highly significant effect of emotion, $F(5,160) = 19.3, p < .001$. Post-hoc comparisons revealed that this was driven by the faster mean response time for happy faces, which was significantly lower compared to all other emotions (all $p < .001$). No other pairwise comparisons were significant. Although the mean response time of the AS group was longer for each emotion, there was no significant effect of group, $F(1,32) = 1.5, p = .23$, or a significant group x emotion interaction, $F(5,160) = .3, p = .93$. In addition, there was no significant correlation between mean emotion recognition score (averaged across all emotions) and mean reaction time for either group (AS, $r = .004, p = .99$; controls, $r = .25, p = .34$). Together, these results confirm the suggestion made in part 1 that emotion recognition deficits in the AS group can not be attributed to a speed-accuracy trade-off.

**Eye-tracking data**

The fixation data were entered into an ANOVA with group as a between-measures variable and phase and emotion as repeated-measured variables. The independent
variable was the percentage of fixations made to the eyes. There was no significant effect of phase or a significant interaction between phase and the other variables (all $F < 1.5$, all $p > .2$); therefore, for display purposes, data from both phases are combined (figure 12).

The main effects of emotion, $F(5,160) = 17.7, p < .001$, and group, $F(1,32) = 5.6, p = .02$, were significant, as was the interaction between them, $F(5,160) = 2.8, p = .02$.

Post-hoc comparisons were used to investigate the main effect of emotion. These revealed that subjects spent significantly less time fixating the eyes when viewing disgusted and angry faces, compared to all other emotions (all $p < .05$, Bonferroni corrected). In addition, subjects spent significantly more time fixating on the eyes when viewing surprised compared to happy faces. No other pairwise comparisons were significant following correction for multiple comparisons.
To investigate the significant group x emotion interaction, t-tests were conducted comparing the groups on each emotion separately. The effects for surprised, $t(1,32) = -2.9$, $p = .02$, sad, $t(1,32) = -2.7$, $p = .03$, and happy, $t(1,32) = -2.6$, $p = .03$, faces were significant, following Bonferroni-Holm correction for multiple comparisons (others: $0.06 < p < .09$).

Data on the amount of time spent fixating the mouth was also entered into an ANOVA with group, phase and emotion as independent variables. Again, the main effect of phase and its interactions with the other variables were not significant (all $p > .1$); therefore data for the different phases are combined for display (figure 13). There was a trend towards the AS group spending more time fixating the mouth than controls but this did not reach
significance, $F(1,32) = 3.5, p = .07$. However, there was again a main effect of emotion,

$$F(5,160) = 7.74, p < .001.$$  

Post-hoc comparisons suggest that this was driven by fewer mouth fixations being made to sad expressions: this was significant in comparison with every other emotion (all $p < .004$, Bonferroni corrected). No other pair-wise comparisons were significant.

**Figure 13.** The amount of time spent fixating on the mouth in the eyetracking task, split by emotion and group. Error bars indicate ± 1 standard error.

For the AS group, the percentage of fixations made to the eyes was negatively correlated with the number made to the mouth, $r = -.66, p = .003$ (figure 14). There was a correlation in the same direction for the control group but this not as strong and was not significant, $r = -.24, p = .36$ (figure 14). These two correlation co-efficients were not significantly different, $z = -1.34, p = .25$.

<table>
<thead>
<tr>
<th></th>
<th>AS Mean</th>
<th>Controls Mean</th>
<th>Total Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Fixations made to the eyes</td>
<td>40%</td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td>% Fixations made to the mouth</td>
<td>60%</td>
<td>50%</td>
<td>55%</td>
</tr>
</tbody>
</table>

**Table 14:** Correlations between group brain activity and amount of anxiety or autistic symptoms, $p < .05$, all other, $p > .25$.
In the AS group, reduced time spent fixating the eyes was not associated with greater severity of autistic symptomology, as measured by either the ADOS or the AQ (table 16). The percentage of fixations made to the mouth showed a trend towards a correlation with AQ but not with the ADOS.

Table 16. Correlations between gaze fixation pattern and measures of severity of autistic symptoms. *p = .07, all others, p > .33
Correlating time spent fixating the eyes with fear recognition score

Next I tested the prediction that poor fear score\textsuperscript{15} in the AS group would be associated with a failure to fixate the eye region of faces by looking at the correlation between these variables separately for each group. Figure 15 shows the relevant scatter plots. There was a significant correlation for the AS group ($r = .56, p = .01$) but not for the control group ($r = .06, p = .41$). However, these correlation co-efficients were not significantly different, $z = 1.29, p = .20$. The correlation for the AS group remained significant even after removal of the outlier seen in the bottom left hand side of the scatterplot ($r = .45, p = .03$).

**Figure 15.** Scatterplots showing the correlation between fixations to the eye region and the ability to recognise fearful faces, shown separately for each group. Fear recognition scores have been averaged across the two repetitions of the test.

\textsuperscript{15} All the emotion recognition scores used in this section are mean scores, calculated from both repetitions of the test.
For the AS group, the amount of time spent fixating the eyes only significantly predicted the ability to recognise fear – not the other emotions (table 17).

### Table 17

<table>
<thead>
<tr>
<th>% fixations made to eyes (mean of all faces)</th>
<th>Recognition score for...</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Happy faces</td>
</tr>
<tr>
<td></td>
<td>r</td>
</tr>
</tbody>
</table>

*Table 17. For people with AS, the amount of time spent fixating the eye region of faces predicts recognition score only for fearful expressions. *p < .06, Bonferroni-Holm corrected.

In the AS group, fear recognition score was predicted by the amount of time spent fixating the eyes of all facial expressions except happy, not just fearful faces (table 18).

### Table 18

<table>
<thead>
<tr>
<th>Percentage of fixations made to the eyes for...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Happy faces</td>
</tr>
<tr>
<td>Mean fear recognition score r</td>
</tr>
</tbody>
</table>

*Table 18. Fear recognition ability is predicted by the amount of time spent fixating eyes of all facial expressions except happy faces. *p < .05, Bonferroni-Holm corrected.

**Discussion**

As predicted, the AS group made fewer fixations to the eyes than did control subjects. This replicates with an AS sample a number of earlier studies, which found the same result with adults diagnosed with autism (Dalton et al., 2005; Klin et al., 2002; Nacewicz et al., 2006; Pelphrey et al., 2002), and is consistent with clinical and anecdotal reports of poor eye fixation in ASDs (for example, see, American Psychiatry Association, 1994; Hutt and Ounsted, 1969).
There was no significant effect of experimental phase or a significant phase x group interaction, suggesting that both groups fixate faces in the same way regardless of whether or not they are overtly engaged in judging the facial expression. There was, however, a significant group x emotion interaction, which post-hoc t-tests suggest is due to a greater difference between the groups when fixating sad, surprised and happy faces compared to the other emotions (see figure 12). Although the post-hoc t-tests for fearful, angry and disgusted faces were not significant following correction for multiple comparisons, there were trends towards significance in each case (see figure 12) and it seems likely that differences between all three emotions contributed to the group difference in the amount of fixations made to the eyes.

Also as predicted, the amount of time spent fixating the eyes correlated with ability to recognise fearful faces in the AS group. A number of previous studies have shown a fear recognition deficit in ASD (Howard et al., 2000; Pelphrey et al., 2002), others have shown that autistic individuals spend less time fixating eyes (Dalton et al., 2005; Klin et al., 2002; Nacewicz et al., 2006; Pelphrey et al., 2002) and we know that eyes are a critical feature for fear recognition in normal subjects (Adolphs et al., 2005; Smith et al., 2005). However, to my knowledge, this is the first study to formally link variability in eye fixation to fear recognition in an ASD.

Fear recognition ability was associated with fixation to the eyes for all facial expressions, not just fearful faces. However, eye fixations only significantly predicted recognition performance for fearful faces, not for other emotions. This is consistent with the data from normal subjects, showing the crucial role of the eyes in recognising fearful faces but not other expressions (Smith et al., 2005, see figure 1) and is reminiscent of SM, who
showed reduced fixation to the eyes for all faces, regardless of emotion, but who has a specific fear recognition deficit (Adolphs et al., 2005).

There were ~4 outliers in the correlation between the percentage of fixations made to the eyes and fear recognition score (see figure 16). These individuals rarely fixated the eyes (making 7 – 14% of fixations to the eyes, compared to a mean of 29% for the AS group and 40% for controls) yet they correctly identified the majority of the fearful faces (mean fear recognition score between 7 and 8 out of 10). These individuals are potentially very interesting because they show that it is possible to achieve a normal fear recognition score without looking at the eyes. These individuals may be using a compensatory cognitive strategy, solving the task in an unusual way, not involving the eyes. This would be consistent with previous studies on other aspects of face processing in ASD, such as face recognition memory, that have shown that individuals with an ASD can perform a given task as well, and sometimes better, than controls, but may be doing so in an atypical fashion (e.g. Langdell, 1978).

One way to investigate if the outliers do possess an alternative strategy (rather than making super-efficient use of the short time they do fixate the eyes) would be to use a

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16 In fact, if their strategy did not involve the eyes (as would seem to be the case) it may add to their low eye fixation percentages by directing them away from the eyes towards other features.
modified Ekman-Friesen test of facial affect in which the eyes had been digitally removed. The hypothesis would be that fear recognition scores would drop in normal controls (and in AS subjects who fixate the eyes normally) but not in the outliers. Another would be to analyse the eye fixation patterns of the outliers in more depth, to see if they consistently make use of certain features other than the eyes when correctly identifying fearful faces\textsuperscript{17}. Probably the most precise, but also most labour-intensive, method of assessing any alternative strategy would be to use the \textit{Bubbles} task (Gosselin and Schyns, 2001; Smith et al., 2005) with these individuals, which would give precise details of the areas of the face that are critical for them to identify a fearful expression. These experiments are beyond the time available for this thesis but they provide interesting avenues for future research.

Both the hypo- and hyper-active amygdala neurodevelopmental models of ASD predict that those with the condition would spend less time fixating eyes than those without the condition and that this would be associated with social-perceptual problems, such as poor fear recognition. However, the models differ in what they would consider to be the root cause of this failure to fixate the eyes. The hypo-activation model would hypothesise that the amygdala fails to flag the eyes as salient and therefore attention is not drawn towards them. The hyper-activation model would predict that fixating eyes produces over-arousal and so they are avoided. In the next section, I attempt to tease apart these possibilities by testing some specific hypotheses of the two neurodevelopmental models.

\textsuperscript{17} A quick analysis of the mouth fixation data does not suggest that the outliers fixate on the mouth more than other low fear scoring AS subjects.
Chapter 5 – Testing predictions from the hyper- and hypo-active amygdala models of ASD

Introduction and summary
In this chapter I will present psychological, psychophysiological and neuroanatomical evidence which, overall, supports the hyper-active amygdala model of ASD and sheds some light on the causes of low eye fixation and poor fear recognition amongst my AS group. The hyper-activity model associates amygdala pathology with anxiety in ASD and predicts that more anxious individuals will show greater avoidance of arousing stimuli. In part 1, I confirm the high incidence of anxiety in AS and show that those individuals with the highest social anxiety fixate the eyes the least and have the lowest fear recognition score. In part 2, I report a psychophysiological experiment in which AS subjects were instructed to fixate either the eyes or the mouths of faces while their skin conductance responses were recorded. The hyper-activation model would predict that individuals who normally show greatest avoidance of the eyes (and the lowest fear scores) will have the greatest autonomic responses to eyes versus mouths. The hypo-active model, which supposes that eyes lack salience for those with an ASD, would predict the opposite effect. The results are not wholly unequivocal but generally support the hyper-active model. In part 3, I present a voxel based morphometry study which looks at the correlation between amygdala volume and social anxiety, eye avoidance and fear recognition in AS. Following Nacewicz et al., (in press), the hyper-activity model predicts that those showing greatest social anxiety and who fixate eyes the least (and therefore have the lowest fear recognition scores) would have the smallest amygdala volumes due to a hyper-activity induced atrophy. The first of these correlations would be inconsistent with
the hypo-active amygdala model; the situation with the latter two is less clear. Evidence is presented for all three correlations, again generally in support of the hyper-active model. Finally, in part 4, I instruct a group of low fear scoring AS subjects to fixate the eyes while viewing faces and examine the effect of this on their ability to recognise fear. The findings as a whole are discussed in terms of the two models and in terms of the limitations of the experimental paradigms. A number of further experiments are proposed, which may help solve some of the remaining ambiguities. In the next chapter, an experiment which explicitly tests a prediction of the hypo-active amygdala model is presented.

**Part 1 – psychological data 1**

The hyper-active amygdala model suggests that the amygdala is involved in producing heightened anxiety in ASD, which results in the avoidance of arousal-inducing stimuli, such as direct gaze. The model therefore predicts that

a) AS subjects will show higher anxiety than controls

b) More anxious individuals will show the greatest avoidance of social stimuli (i.e. lowest fixation of the eyes) and therefore the lowest fear recognition scores.

The major aim of this section is to test these predictions via self-report questionnaires of general and social anxiety.

In chapter 3 I reported that normal males who were poor at recognising fear (LFS) had a distinctive personality profile when compared to males who had no deficit recognising fear (NFS). As well as rating themselves higher for ‘neuroticism’ (which is related to anxiety) they also rated themselves as less ‘open to experience’. Therefore, a secondary
aim of this section is to see if ‘openness to experience’ plays a part in the fear recognition deficits of the AS group.

Method
The subjects who took part in the eyetracking experiment reported in chapter 4 were contacted by post and asked to fill in the NEO PI-R personality questionnaire (Costa and McCrae, 1991) and two other questionnaires, measuring aspects of anxiety: the trait portion of the Spielberger state-trait anxiety questionnaire (Spielberger, 1983) and the Social Phobia and Anxiety Inventory (Turner et al., 1999).

Social desirability, i.e. the tendency to portray oneself in a favourable light, is known to bias anxiety measures, often leading to a underestimation of an individual’s true value on this dimension (Egloff and Schmukle, 2003). To control for this confound, subjects were also asked to fill out the Marlowe-Crowne social desirability scale (Crowne and Marlowe, 1960) and this measure was entered as a co-variate in the statistical analyses. Seventeen of the AS subjects and fourteen of the control subjects replied to the request to fill out questionnaires.

Results

Personality and anxiety measures
Figure 17 shows how the subjects rated themselves on the five factors of the NEO PI-R.

Figure 17. Personality characteristics of the AS and control groups. Error bars show ±1 standard error.
personality questionnaire. These data were entered into a MANOVA. There was a highly significant overall difference between the groups: Pillai’s trace = .99, $F(5,24) = 759$, $p < .001$. The data suggest that this is driven by differences in neuroticism and extraversion between the two groups (figure 17), which was confirmed by ANOVAs conducted on each personality factor separately: neuroticism, $F(1,28) = 22.5$, $p < .001$; extraversion, $F(1,28) = 9.7$, $p = .004$; all others, $F < .6$, $p > .4$.

It is important to note that, unlike the LFS group seen in chapter 3, AS subjects did not rate themselves lower in terms of ‘openness to experience’. In addition, fear recognition scores did not correlate significantly with openness to experience rating for either AS participants ($r = .21$, $p = .42$) or controls ($r = .10$, $p = .75$). The same is true for extraversion – AS group, $r = .001$, $p = .99$; control group, $r = -.11$, $p = .77$.

Table 19 summarises how the groups rated themselves on the anxiety questionnaires and on the social desirability scale. There was a trend towards a significant difference in social desirability ratings: $t(29) = -1.94$, $p = .06$, with controls tending to portray themselves in a more positive light than the AS group. AS subjects rated themselves significantly higher on both anxiety questionnaires, with social desirability entered as a co-variate: trait anxiety, $F(1,28) = 12.1$, $p = .002$, Bonferroni-Holm corrected; social phobia scale, $F(1,28) = 10.2$, $p = .004$, corrected.
However, within the AS group, none of the anxiety measures (including neuroticism) correlated significantly with the severity of autistic symptoms, as measured by the ADOS and AQ (table 20).

<table>
<thead>
<tr>
<th></th>
<th>ADOS Com</th>
<th>ADOS RSI</th>
<th>ADOS Total</th>
<th>AQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trait Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>r</em></td>
<td>.38</td>
<td>.38</td>
<td>.40</td>
<td>.31</td>
</tr>
<tr>
<td><em>p</em></td>
<td>.15</td>
<td>.15</td>
<td>.13</td>
<td>.25</td>
</tr>
<tr>
<td><strong>Neuroticism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>r</em></td>
<td>.02</td>
<td>.03</td>
<td>.03</td>
<td>-.44</td>
</tr>
<tr>
<td><em>p</em></td>
<td>.94</td>
<td>.91</td>
<td>.92</td>
<td>.09</td>
</tr>
<tr>
<td><strong>Social Phobia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>r</em></td>
<td>-.22</td>
<td>-.13</td>
<td>-.17</td>
<td>.04</td>
</tr>
<tr>
<td><em>p</em></td>
<td>.42</td>
<td>.62</td>
<td>.52</td>
<td>.88</td>
</tr>
</tbody>
</table>

**Table 20.** Correlations between the anxiety measures and the severity of autistic symptoms.

ADOS = autism diagnostic observational schedule. ADOS Com = communication sub-scale of the ADOS. ADOS RSI = reciprocal social interaction subscale of the ADOS. AQ = autistic spectrum quotient

**Social phobia predicts poor fear recognition and low fixation of the eyes in AS**

For the AS group, social phobia showed a significant negative correlation with mean fear recognition score after controlling for differences in the social desirability scale (table 21 and figure 18). For controls, there was a positive correlation with trait anxiety, again after controlling for social desirability rating (table 21). There were no other significant correlations.
Table 21. Partial correlations between anxiety measures and mean fear recognition score, controlling for social desirability scale (SDS). * = p < .05

Figure 18. Scatterplot showing the correlation between social phobia and fear recognition in AS subjects, after controlling for the social desirability scale (SDS). The residuals after regressing social phobia onto SDS are plotted against the residuals after regressing mean fear recognition score onto SDS.

In the AS group, social phobia also correlates with the percentage of gaze fixations made to the eyes, again after controlling for SDS (table 22 and figure 19).

Table 22. Partial correlations between anxiety measures and the percentage of fixations made to the eyes, controlling for social desirability scale (SDS). * = p < .05

Figure 19. Scatterplot showing the correlation between social phobia and the percentage of fixations made to the eyes in AS subjects, after controlling for the social desirability scale (SDS). The residuals after regressing social phobia onto SDS are plotted against the residuals after regressing the mean percentage of fixations made to the eyes score onto SDS.
The correlations between social anxiety, the amount of time spent fixating the eyes and fear recognition ability in AS are summarised in figure 20. These results will be discussed at the end of the chapter, together with those from parts 2 and 3.

![Diagram showing relationships between social anxiety, percentage of fixations made to the eyes, and fear recognition ability.](image)

**Figure 20.** Summary of the relationships between social anxiety, the amount of time spent fixating the eyes and fear recognition ability in AS.

**Part 2 – psychophysiological data**

I have shown that poor fear recognition score in AS is associated with a failure to fixate the eye region of faces. Both of these variables are in turn associated with heightened social anxiety. This evidence is consistent with the hyper-responsive amygdala model of ASD, which predicts that some subjects with AS would find social stimuli, such as eyes, aversive and so actively avoid them, leading to social-perceptual deficits. To further test this model I conducted an experiment where AS subjects were told to engage the eyes or the mouth of faces while their skin conductance responses were measured. According to the hyper-responsive model, the prediction would be that those subjects who normally engage the eyes the least (and who have the lowest fear scores), should show the highest autonomic response when instructed to engage the eyes versus the mouth. By contrast, the hypo-responsive model suggests that those who fail to fixate the eyes do so because the stimuli lack salience for them. Therefore, the prediction from this model is the
opposite of the hyper-active model: those who normally engage the eyes the most (and have the highest fear scores) should show the greatest autonomic reaction when made to look at eyes versus the mouth.

**Methods**

The same seventeen individuals with AS who took part in part 1 of this chapter also took part in the psychophysiological experiment. Figure 21 summarises the experimental design. There were 8 experimental blocks, during each of which subjects viewed 14 faces from the KDEF (Lundqvist and Litton, 1998) series - 7 male, 7 female, 2 of each of the 6 ‘basic’ emotions plus 2 neutral faces. Faces were presented for 1.5 seconds, interspersed with a blank, grey screen for 0.5 seconds. For half the blocks, subjects were instructed to fixate on the eyes for the whole block, for the other half they were told to fixate the mouth region. As I was interested in correlations within the group, it was important that any order effects that existed were kept constant for each subject; therefore blocks were shown in a fixed order (see figure 21). Before each block, subjects were presented with a 3 second prompt, which instructed them to fixate either the eyes or the mouth region. This was followed for two seconds by two adjacent fixation crosses, which were placed either where the eyes were to appear or where the mouth was to appear, depending on the experimental condition. After each block, a blank grey screen was presented for 35 seconds. This led to an inter-block time of 40 seconds, a block time of 28 seconds and a total experiment time of 9 minutes 4 seconds. There was no experimental task.

During each block, subjects’ skin conductance responses and eye movements were recorded following the procedures described in chapter 2. Subjects’ eye fixations were monitored carefully during the experiment to ensure that they fixated on the eyes or
mouth as appropriate. If required, during the rest period subjects were reminded to fixate the appropriate area when instructed to do so. However, this rarely proved necessary.

The total number of SCRs and the total amplitude of SCRs were calculated for each condition. For statistical analyses, the total amplitude of SCRs were normalised via a square root transformation. However, for ease of interpretation, it is the raw data that is presented in table 23.

Figure 21. Measuring autonomic responses to eyes in AS – experimental design.
Results

Table 23 summarises the SCR responses to eyes and mouths. The difference in response between eyes and mouths is significant for the sum amplitude of SCRs, \( t(16) = 2.4, p = .03 \), but not for the absolute total of SCRs, \( t(16) = 1.1, p = .2 \).

As table 24 and figure 22 show, the level of reported social phobia correlates well with the difference in the absolute number of SCRs between the eyes and the mouth condition (N difference) but not with the difference in the sum amplitude of SCRs between the eyes and the mouth (sum difference).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of SCRs to eyes</td>
<td>2.1</td>
<td>2.11</td>
</tr>
<tr>
<td>Sum of SCRs to mouth</td>
<td>1.1</td>
<td>.86</td>
</tr>
<tr>
<td>Sum difference</td>
<td>1.0</td>
<td>1.85</td>
</tr>
<tr>
<td>N SCRs to eyes</td>
<td>10.6</td>
<td>7.19</td>
</tr>
<tr>
<td>N SCRs to mouth</td>
<td>9.8</td>
<td>6.52</td>
</tr>
<tr>
<td>N difference</td>
<td>.8</td>
<td>3.02</td>
</tr>
</tbody>
</table>

Table 23. SCR responses to eyes and mouths. 'Sum of SCRs' is the total amplitude in \( \mu \text{Siemens} \). 'N scrs' refers to the absolute number of SCRs.

Table 24. Correlations between skin conductance responses and the level of reported social phobia.

Figure 22. Scatterplot of the correlation between social phobia and N difference.
Similarly, as presented in table 25 and figure 23, N difference correlates negatively with the percentage of fixations made to the eye region (eye tracking data from chapter 4), whereas sum difference does not.

![Graph](image)

**Table 25.** Correlations between skin conductance responses and the percentage of fixations made to the eyes.

**Figure 23.** Scatterplot of the correlation between N difference and the percentage of fixations made to the eyes.

However, the level of autonomic reaction to eyes did not correlate with the severity of autistic symptoms, as measured by the ADOS and AQ (table 26).

<table>
<thead>
<tr>
<th></th>
<th>ADOS Com</th>
<th>ADOS RSI</th>
<th>ADOS Total</th>
<th>AQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum difference</td>
<td>$r$ .17</td>
<td>.03</td>
<td>.09</td>
<td>.35</td>
</tr>
<tr>
<td></td>
<td>$p$ .54</td>
<td>.93</td>
<td>.75</td>
<td>.22</td>
</tr>
<tr>
<td>N difference</td>
<td>$r$ .06</td>
<td>.19</td>
<td>.18</td>
<td>.32</td>
</tr>
<tr>
<td></td>
<td>$p$ .83</td>
<td>.50</td>
<td>.51</td>
<td>.27</td>
</tr>
</tbody>
</table>

**Table 26.** Correlations between the autonomic measures and the severity of autistic symptoms.

ADOS = autism diagnostic observational schedule. ADOS Com = communication sub-scale of the ADOS. ADOS RSI = reciprocal social interaction subscale of the ADOS. AQ = autistic spectrum quotient.

Unfortunately, although the eyetracker was used during this experiment and gaze patterns were monitored carefully in real-time to ensure that subjects were looking at the required...
parts of the face, the traces were lost due to recording error and it is therefore not possible to present data on where the subjects were looking.

**Part 3 – Neuroanatomical evidence**

As discussed at length in chapter 1, existing structural studies of the amygdala in ASD support a dynamic model in which abnormally large amygdala volumes in childhood give way to abnormally small amygdala volumes by adulthood. Severity of impairment is thought to interact with age, diminishing the observed changes in higher-functioning individuals. Drawing on animal models of chronic stress, Nacewicz et al. (*in press*) propose that the initial outgrowth followed by atrophy is induced by neuronal hyperactivity, caused by heightened ‘allostatic-load’ (Nacewicz et al. *in press*, pg. 20). In support of this, they find that a group of autistic adults not only has a reduced mean amygdala volume but that those individuals with the smallest amygdala spend the least time fixating the eyes of faces in an eye-tracking task. In this section, I attempt to replicate and extend the work of Nacewicz et al. (*in press*) with my sample of AS subjects. Specifically, I aim to answer the following questions:

a) Is there an overall group difference in amygdala volume between AS subjects and age and IQ matched controls? Given the age x impairment interaction discussed above, and the fact that my group are high-functioning, I predict that there will not be such a difference. Rather, the informative data will come from examining the variability of amygdala volumes within the group.
b) Is there a correlation between amygdala volume and the percentage of fixations made to the eyes in AS, as there was in the low-functioning autism group tested by Nacewicz et al. (in press)?

c) The logical extension of (b) is that the individuals with the smallest amygdala volume should be poorest at recognising fearful faces. This is also tested.

d) Nacewicz et al. (in press) propose that amygdala atrophy is being caused by heightened allostatic load. Therefore, do the AS participants with the smallest amygdala show:
   a. the highest level of social anxiety?
   b. the greatest autonomic activity when looking at eyes compared to mouths?

e) A number of authors have found a negative correlation between amygdala volume and severity of autistic impairment, as measured by the ADI-R. I will look for a similar correlation within my sample using the ADOS and AQ.

**Methods**

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Sex</th>
<th>ADOS Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>31.4 (12.91)</td>
<td>13 M</td>
<td>5 Autism 10 Autistic spectrum</td>
</tr>
<tr>
<td>Controls</td>
<td>31.8 (11.28)</td>
<td>13 M</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Participants**

Fifteen subjects with AS took part in this section of the study, along with fifteen age matched controls. A number of these controls were new subjects who had not participated in any previous experiments. Table 27 gives the group characteristics.
**Imaging procedures**

MRI was performed using a Siemens 1.5T scanner. A phased-array head coil was used to obtain high-resolution images using a T1 weighted sequence yielding 124 contiguous 1.6mm axial slices of 256 x 256 voxels with an in-plane resolution of 1 mm².

**Analysis**

SPM5 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) was used for both the pre-processing and statistical analysis steps. Pre-processing followed the procedures explained in chapter 2. Briefly, images were normalised to the MNI template and segmented into grey matter, white matter and CSF images as part of a unified segmentation model (Ashburner and Friston, 2005). The data was then smoothed using a 12mm Gaussian kernel. A smoothing parameter of 12mm was chosen because it corresponds roughly to the cross-sectional dimensions of the amygdala and, by the matched filter theorem, sensitised the analysis to differences at this spatial scale (Salmond et al., 2003).

There is some evidence that global brain volume is enlarged in ASD (e.g. Courchesne and Pierce, 2005a; Palmen et al., 2006). Therefore, in volumetric studies focussing on a specific region of interest, it is necessary to control for this confound. In this study, grey matter, white matter and CSF volumes were determined by finding the integrals of the relevant images. Total brain volume was found by summing these volumes for each participant.

To compare group differences, an ANCOVA model was used, with total brain volume as a covariate. To look for correlations, a regression model was used. To correct for multiple comparisons, small volume correction was employed, centred on the amygdala (left and

Results

Group differences

Table 28 summarises the grey matter, white matter, CSF and total brain volumes for the two groups. There were no significant differences between group means (all $p > .37$). However, the AS group showed significantly greater variability in both grey matter volume, $F(1, 28) = 17.6, p < .001$, and total brain volume, $F(1, 28) = 12.6, p = .001$ – see column four in table 26 and figure 24.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM Vol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>.77</td>
<td>.04</td>
</tr>
<tr>
<td>AS</td>
<td>.79</td>
<td>.11</td>
</tr>
<tr>
<td>WM Vol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>.49</td>
<td>.04</td>
</tr>
<tr>
<td>AS</td>
<td>.48</td>
<td>.06</td>
</tr>
<tr>
<td>CSF Vol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>.28</td>
<td>.06</td>
</tr>
<tr>
<td>AS</td>
<td>.31</td>
<td>.10</td>
</tr>
<tr>
<td>Brain vol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>1.53</td>
<td>.07</td>
</tr>
<tr>
<td>AS</td>
<td>1.58</td>
<td>.19</td>
</tr>
</tbody>
</table>

Table 28. Volumes of neural tissue in AS and control groups.

Values are in litres. GM = grey matter, WM = white matter, CSF = cerebro-spinal fluid.

To look for regional differences in grey matter, the smoothed, segmented grey matter images were entered into an ANCOVA in SPM5, with group as a fixed factor and total brain volume as a covariate. In the amygdala (the \textit{a priori} region of interest) there were no significant differences in either direction, even at liberal thresholds ($p < .01$, uncorrected). In other areas of the brain there were no significant differences between the groups after correcting for multiple comparisons.
Figure 24. Box plots showing the distribution of grey matter and total brain volume in the AS and control groups. There is significantly greater variability in both measures for the AS group (see main text). Boxes show the median (black line) and the inter-quartile range (IQR, edges of boxes). Whiskers are 1.5 * IQR. Circles represent mild outliers (between 1.5 and 3 * IQR) and stars represent extreme outliers (> 3 * IQR).

Correlations

Next, for the AS subjects, I looked for correlations between grey matter volume and the following four variables:

1. the percentage of gaze fixations made to the eyes (taken from the eyetracking experiment in chapter 4)
2. mean fear recognition ability (again taken from experiment 4)
3. social phobia score
4. autonomic response to eyes compared to mouths – ‘N difference’ from part 2 of this chapter

focusing the analysis on the amygdala. Following small volume correction, there were significant correlations in each case for the left, but not the right, amygdala (table 29). Weaker correlations with grey matter volume were evident in the right amygdala, but they did not survive small volume correction.
I also looked for correlations between amygdala grey matter volume and the severity of autistic symptoms, as measured by the ADOS and AQ. There were no significant voxels either at $p < .05$ SVC or at $p < .001$ uncorrected.

**Part 4 – psychological data 2**

The work presented so far has assumed that not looking at the eyes causes poor fear recognition. However, while the data provided in chapter 4 are consistent with this hypothesis, they are correlational and so it is not possible for this to be positively inferred. Proving causation in this manner can often be difficult, but one possibility is to borrow an experiment from Adolphs et al.’s (2005) study of SM. While SM does not spontaneously look at the eyes, she is able to do so when instructed, with the result of a dramatic improvement in her fear recognition ability. When the task is repeated a few weeks later, however, both the failure to fixate the eyes and the poor fear score have returned. Together, these results suggest that amygdala damage in SM has caused a failure to spontaneously fixate the eyes, which is the mechanism for her poor fear recognition.

However, there is an important caveat to bear in mind with this experiment. As Adolph et al. (2005) suggest, SM is likely to have had the opportunity, before her lesion, to learn the

<table>
<thead>
<tr>
<th>Variable</th>
<th>MNI co-ordinate of maximum activation</th>
<th>$p$ value (SVC)</th>
<th>$\text{Pearson}{'}s$ $r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>% fixations to the eyes</td>
<td>$-18, -3, -25$</td>
<td>.037</td>
<td>.60</td>
</tr>
<tr>
<td>Mean fear recognition score</td>
<td>$-17, -4, -20$</td>
<td>.028</td>
<td>.62</td>
</tr>
<tr>
<td>Social phobia</td>
<td>$-26, -2, -26$</td>
<td>.014</td>
<td>-.74</td>
</tr>
<tr>
<td>N difference</td>
<td>$-19, -3, -21$</td>
<td>.038</td>
<td>-.59</td>
</tr>
</tbody>
</table>

*Table 29. Correlations with amygdala grey matter volume in AS.*
association between eyes and fear. This explains how, when she is made to look at eyes, SM has the necessary cognitive representations to be able to link the visual input to its meaning. However, the situation may be different with ASD: the hypo- and hyper-active amygdala models assume that lack of attention towards socially salient stimuli exists from birth (e.g. Schultz, 2005), i.e., unlike SM, AS subjects may never have had the opportunity to learn the association between the eyes and fear. In other words, even though not fixating the eyes may ultimately be the cause of poor fear recognition in some AS subjects, directing their attention towards the eyes may not dramatically improve their ability because they may not formed the mental representations necessary to make adequate use of the data.

To summarise, if low fear scoring AS subjects are made to look at the eyes in faces and, like SM, their fear recognition ability does dramatically improve, this would suggest:

a) Failure to spontaneously fixate eyes is the mechanism for poor fear recognition

b) The subjects do possess the necessary mental representations to make use of information from the eyes when they receive it. Like SM, their problem seems to be one of not receiving the necessary input rather than not being able to adequately process that input. This would perhaps argue against the neurodevelopmental account of social-perceptual impairment given by the hypo- and hyper-active amygdala models.

If, when made to look at the eyes, low fear scoring AS subjects' fear recognition ability does not show a strong improvement, this could mean one of two things:

---

18 However, it should be noted that the date of SM’s lesion is uncertain and there is a possibility that it was sustained early in life (Adolphs et al., 1995).
a) Failure to spontaneously fixate the eyes is not the mechanism for poor fear recognition in AS.

b) Alternatively, failure to fixate the eyes is the cause, but is so developmentally rather than in real-time. This would support the neurodevelopmental account given by the hypo- and hyper-active amygdala models.

In this section I will present some preliminary data on a repeat of the Adolphs et al. (2005) study with some of the low fear scoring AS subjects.

**Method**

Ten of the AS subjects with the lowest average fear scores took part. Unfortunately, three subjects with low fear scores were not available to take part.

Subjects repeated the Ekman-Friesen test of facial affect but were this time asked to fixate the eyes in the faces throughout the presentation. The eye tracker was used to monitor where subjects were looking during the experiment and encouragement was given to look at the eyes if necessary.
Results

Table 30 compares the fear score during free viewing to that when subjects were made to look at the eyes. As can be seen from this table, with one or two exceptions, fear recognition scores did not improve strongly. The mean score in the free viewing tasks was 6.35/10, when made to look at the eyes this rose to 6.9/10, a difference which was not significant – *t*(9) = -1.2, *p* = .26.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean free viewing fear score</th>
<th>Fear score when made to look at eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>6</td>
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<tr>
<td>4</td>
<td>6.5</td>
<td>7</td>
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<tr>
<td>5</td>
<td>6.5</td>
<td>10</td>
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<td>7.5</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>7.5</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 30. The effect of being encourage to fixate the eyes on fear recognition of low fear scoring AS subjects. The ‘mean free viewing fear score’ is the mean calculated form both repetitions of this test.

Discussion of parts 1 - 4

In this chapter I have presented psychological, psychophysiological and neuroanatomical evidence which begins to converge on an explanation for the poor fear recognition ability amongst some people with AS (see figure 25) and which, broadly speaking, offers support for the hyper-activity amygdala model of ASD. The main causal pathway is proposed to be as follows: in some AS subjects, from early in life, eyes are hyper-arousing (which is aversive) and are therefore avoided. Because the eyes are a critical feature for recognising a fearful face (Adolphs et al., 2005; Kohler et al., 2004; Smith et al., 2005), these subjects fail to make the necessary associations linking eyes to fearful faces and so have a pervasive fear recognition deficit. Associated with the hyper-arousal to social stimuli is heightened social anxiety and smaller amygdala volume. According to
the hyper-active amygdala model, the latter is due to neuronal atrophy caused by high ‘allostatic load’, in a similar fashion to atrophy seen in rat models of chronic stress (Nacewicz et al., in press). Whether reduced amygdala volume has a direct role to play in the reduced time spent fixating the eyes and/or the poor fear recognition ability is unclear and has not been explicitly considered in descriptions of the hyper-active amygdala model (e.g. Nacewicz et al., in press). However, it is a possibility and is discussed further later in this chapter.

In part 1, I confirmed the higher incidence of anxiety (general and social specific) in AS and showed that those subjects who displayed the highest levels of social anxiety:

a) spent least time fixating the eyes of faces

b) had the lowest fear recognition scores.
This is consistent with the idea, predicted by the hyper-activity model, that eye avoidance in ASD is linked to hyper-arousal and anxiety in social situations. However, against predictions, neither general (trait) anxiety or neuroticism measures showed these correlations (although neuroticism showed a trend in the right direction). Eyes and faces are archetypal social stimuli so perhaps it is unsurprising that stronger relationships were found with social rather than general anxiety. Still, it will be useful to see replications of these findings, with new samples of participants, before confident conclusions can be drawn.

As discussed in chapter 1, there is a large literature showing that anxious people are hypervigilant for potentially threatening stimuli, such as fearful or angry faces (for review see Dalgleish and Power, 1999). For example, anxious individuals have an attentional bias for fearful faces (Fox et al., 2005; Georgiou et al., 2005) and samples of high trait (general) anxiety (Surcinelli et al., 2006) and high social anxiety individuals (Richards et al., 2002) show an advantage for recognising fear in facial expressions. Consistent with this, I found that trait anxiety correlated positively with fear recognition in my control group and that neuroticism and social anxiety showed a trend in the same direction. However, these findings are clearly inconsistent with my results for the AS group and with the predictions made by the hyper-active amygdala model of ASD, under which individuals are supposed to avoid anxiety-inducing stimuli rather than being biased towards them. This discrepancy may reflect an interaction between autistic symptoms and anxiety. In other words, people with an ASD might react to and cope with their anxiousness in a different way than non ASD people. Consistent with this, Pfeiffer et al. (2005) suggested that anxiety may produce sensory defensiveness in high-functioning autistics, rather than hyper-vigilance. More work needs to be done to assess these
potential differences in coping style, for which qualitative interviews may be the most appropriate method.

Another potential explanation for the apparent discrepancy between my AS findings and those of the hyper-vigilance literature relates to the actual level of anxiety involved in these different investigations. For example, Richards et al. (2002) use the same measure of social anxiety as I do in my studies with AS (the SPAI, Turner et al., 1999). They find that their high socially anxious group are better at recognising fearful faces than their low social anxiety group. However, their high social anxiety group has a mean SPAI of 84.1 \((SD = 11.9)\), which corresponds to the minimum SPAI score for my AS group (mean = 101.1, \(SD = 17.9\)). The AS subjects scoring ~84 on the SPAI in my study are the subjects with the highest fear scores, who spend the most time fixating the eyes— it is the AS individuals with very high SPAI scores (>110) who have the low fear scores and fixate the eyes the least. Furthermore, the low social anxiety group reported by Richards et al. (2002), who are poor at recognising fear, have very low SPAI scores (mean = 19.3, \(sd = 7.7\), bottom 25% of the normal population), much lower than my control sample (mean SPAI score of 65.5, \(sd = 46.8\)). These findings are suggestive of a non-linear relationship between social anxiety and fear recognition / hyper-vigilance. The shape of the relationship might follow an inverted ‘U’ (see figure 26), such that low socially anxious individuals are hypo-vigilant of threatening
stimuli (such as a fearful faces), medium-high socially anxious individuals – represented by the high anxious group of Richards et al. (2002) and the lower socially anxious AS subjects in my study – are hyper-vigilant and are therefore good at recognising fear. But when socially anxiety becomes very high, as in some of my AS participants, hyper-vigilance may give way to sensory defensiveness and avoidance, resulting in a falling off of fear recognition. It would be interesting to conduct a study with a large sample of normal individuals to look for evidence of this kind of non-linear relationship.

In chapter 3, I found that males from the normal population who were poor at recognising fear (LFS) rated themselves as less open to experience than did males with a normal fear recognition ability (NFS). Other studies have also shown a relationship between greater openness to experience and the ability to recognise emotions (Matsumoto et al., 2000; Terracciano et al., 2003). However, variability on this dimension of personality did not appear to have a role in the fear recognition deficits in AS: there was no difference between the AS group and controls and no correlation between openness and fear score within the group.

The psychophysiological experiment presented in part 2 of this chapter offered the best chance to directly test the hyper- against the hypo-active amygdala models of ASD. If some individuals with AS are avoiding eyes because they find them aversive (as predicted by the hyper-active model) then this should be detectable via autonomic measures: those who normally avoid the eyes should show the greatest autonomic response when they are made to look at eyes. By contrast, the hypo-active model suggests that a lack of eye contact results from a failure to flag the eyes as salient, therefore those who normally fail to fixate the eyes should show the smallest autonomic response when they are made to look at eyes. I found some support for the former: a greater difference
between the total number of SCRs produced when looking at the eyes compared to when looking at the mouth was associated with greater social phobia and less time spent fixating the eyes.

However, the data using the total SCR amplitudes failed to show these correlations. While this makes it difficult to form definitive conclusions from the data, it is important to note that both measures failed to support the hypo-active model: there were no positive correlations between either measure of the autonomic response to eyes and either eye fixation percentage or fear score. Therefore, the data broadly support the predictions from the hyper-active model. Still, it would be useful to repeat the experiment with an improved paradigm, designed to be more sensitive to the potential responses. Some suggestions are given below.

A problem with this and many studies of autonomic responses is the rapid onset of habituation (possibly made worse by the 'unreal' nature of laboratory based stimuli – see next paragraph). A more sensitive approach may have been to use an odd-ball paradigm in which grey screens, blank except for fixation crosses corresponding to either the eyes or the mouth, were interspersed randomly with faces. This would mean that the appearance of each face would retain a level of surprise, which may diminish the affect of habituation.

Another potential problem with the psychophysiological experiment may have been a lack of ecological validity. When the subjects were debriefed following the experiment, a number admitted to having an aversion to eyes in real-life social situations but to not feeling any such revulsion during the experiment because they "knew that it was just a picture". In future experiments it might be valuable to attempt to recreate a more realistic
social situation, perhaps by recording SCRs while subjects fixate on the eyes of real people.

Another problem is that, because of recording error, I was unable to make use of the eyetracking data I took during the psychophysiological task. It would have been useful to make sure that the subjects were indeed fixating the eyes when they were instructed to. The amount of time they did spend fixating the eyes could have been used as a co-variate in the statistical analyses. However, during the experiment I was able to carefully monitor where the subjects were looking using the eyetracker and to offer encouragement if subjects forgot to fixate the required area. This was almost never necessary and it is unlikely that, were it available, the eyetracking data would make a significant difference to the findings.

In part 3 of this chapter, I presented neuroanatomical evidence which again broadly supported predictions made by the hyper-active model. Nacewicz et al. (in press) suggest that, by adulthood, hyper-arousal to social stimuli in AS causes hyper-activity induced amygdala atrophy. In support of this they found that autistic individuals who fixate the eyes the least have the smallest amygdala volume. I replicated this finding in my sample of high-functioning adult AS subjects and extended it by showing that small amygdala volume is also associated with:

a) greater autonomic arousal to eyes
b) greater social anxiety
c) lower fear recognition score

These data are consistent with hyper-activity induced atrophy of amygdala neurons resulting from heightened allostatic load. However, to infer the developmental pattern of these changes, longitudinal studies will be required.
It is unclear whether, or to what extent, smaller amygdala volume has a role in causing reduced fixation of the eyes and/or poor fear recognition in some AS subjects. It could simply be that these variables all correlate with the hyper-arousal to social stimuli, which may be the primary causal factor. Alternatively, it could be a combination: initially, reduced fixation of the eyes could be due, alone, to the hyper-arousal caused by such stimuli but amygdala atrophy, as it progresses, could add an effect of its own. Assuming the hyper-active amygdala model is correct, a longitudinal study may help decide between these possibilities. According to the model, hyper-arousal to social stimuli is present early in life but amygdala atrophy only becomes apparent in late adolescence or adulthood. If this model is correct and the atrophy itself is having a causal effect on abnormal gaze patterns and/or fear recognition impairment, then these factors (the eye fixations and fear recognition) should get worse with age, as the atrophy progresses.

In part 4 of this chapter I showed that the majority of low fear scoring AS subjects show only a small or no improvement in fear recognition ability when they are instructed to look at the eyes. This is in contrast to SM, who improved from 46% of fearful faces correctly identified to 83%, with this simple instruction (Adolphs et al., 2005). One interpretation of this finding is that failure to fixate the eyes is not causing poor fear recognition in AS and that the correlation between these variables is perhaps due to a third, as yet unidentified, factor. However, as explained in the introduction to part 4 of this chapter, these findings are also consistent with the developmental account of social-perceptual impairment which is proposed for the hyper- (and the hypo-) active amygdala models. The models assume that lack of attention towards socially salient stimuli, such as eyes, occurs from birth (e.g. see Schultz, 2005). This is thought to lead to underdevelopment of social-perceptual abilities and their associated brain regions such that low fear scoring AS subjects may not possess the mental representations required to
adequately process the visual input even if they are directed towards the eyes. This is in contrast to SM who, Adolphs et al. (2005) suggest, is likely to have had the opportunity to accrue social knowledge prior to her lesion.

Caveats and future experiments

There are two important and related caveats with the interpretation put forward so far. If the hyper-activity model does apply in the way stated above, it clearly does not apply equally to all individuals with AS. AS subjects vary from normal to abnormal on all the measures presented. On its own this would not necessarily be a problem – one could posit that more severely autistic subjects showed the necessary signs more clearly. However, this brings us to the second caveat: neither fear recognition ability, the percentage of time spent fixating the eyes, autonomic responses to the eyes nor the amount of amygdala atrophy, correlated with the severity of autistic symptoms, as measured by the ADOS and AQ. This is in contradiction to Nacewicz et al. (in press), who found that autistic symptoms correlated negatively with both time spent fixating the eyes and amygdala volume. However, the participants in the Nacewicz et al. (in press) study were low functioning individuals with autism, in contrast to my high-functioning AS group. In addition, Nacewicz et al. (in press) used the ADI-R as a measure of the severity of autistic symptoms. I was unable to take a similar measure with my group due to the unavailability of parental informants for a number of subjects. If I had used a parental interview it is possible that I would have found the required correlations – the ADI-R is more dimensional that the ADOS and does not rely on self-report, unlike the AQ. However, this seems unlikely as all three measures have been clinically validated to measure the same construct (Baron-Cohen et al., 2001b; Lord et al., 1994; Lord et al., 1999) and it would raise the question of how to interpret my ADOS and AQ results.
Another possibility is that the model presented in figure 25 represents a route to social perceptual impairment which can exist independently from other routes that lead to the symptoms picked up by classic diagnostic tools, such as the ADOS. I showed in chapter 3 that poor fear recognition and associated low fixation of eyes can exist without an increase in the presence of autistic symptoms: LFS did not score higher than NFS on the AQ. This is a difficult issue, which will considered in greater detail in the general discussion.

Another caveat is that, while much of the evidence presented here is more consistent with predictions of the hyper-active model, there is little which argues positively against the hypo-active model. For example, the hypo-active model does not explicitly predict a relationship between failing to fixate the eyes and heightened social anxiety but it is not clear that it would predict its absence. Similarly for the neuroanatomical data, the correlation between social anxiety and smaller amygdala volume clearly favours the hyper-active model but one could envisage an argument whereby reduced salience of social stimuli is related to small amygdala volume via under-use and under-development of amygdala neurons. The psychophysiological experiment offered the best hope of providing evidence positively for one theory of the other. The results, however, were not wholly unequivocal (the correlations predicted by the hyper-active model existed for N difference but not sum difference) so some residual doubt remains. A solution would be to repeat the autonomic experiment with a more sensitive and ecologically valid paradigm. Another would be to use fMRI to directly measure amygdala activity in ASD while manipulating the focus of gaze. Unfortunately, there is not time to conduct these experiments within the current program but they provide the logical next step for the future. Instead, for the remaining results chapter of this thesis I will present an
experiment which aims to explicitly test a prediction from the hypo-active amygdala theory of ASD.
Chapter 6 – Testing the hypo-active amygdala model of ASD

Summary

Identification of a 1st target in a rapid serial visual presentation sequence leads to a transient impairment in the ability to report a 2nd target – this is known as the attentional blink (Raymond et al., 1992). The size of the attentional blink is substantially reduced if the second target is emotionally arousing (Anderson, 2005; Anderson and Phelps, 2001; Ogawa and Suzuki, 2004). A functioning amygdala is critical for this emotional modulation of the attentional blink and the phenomenon is thought to represent a specific example of the amygdala's role in enhancing perception of emotionally or socially salient events (Anderson and Phelps, 2001). The hypo-active amygdala model of ASD cites a failure in the amygdala to perform this perception-enhancing role as a primary cause of the social-perceptual problems in the disorder (Schultz et al., 2000b; Schultz, 2005). Using an emotional modulation of the AB paradigm, I found, against the predictions of the hypo-active model, that subjects with AS did show a perceptual benefit for arousing stimuli in general. However, the size of this benefit was significantly reduced compared to controls when the lag between the first and second target was very short – i.e. when attention was most stretched. Control experiments showed that this finding could not be attributed to differences in the perceived arousal of the stimuli or to a global impairment affecting any type of modulation of perceptual encoding at short inter-target lags. The results are discussed in terms of the hypo-active amygdala model of ASD and in the context of the other findings presented in this thesis.
Introduction

Many theorists argue that the amygdala functions as a ‘salience’ detector, monitoring the environment for emotionally or socially significant events and then influencing current and future behaviour through modulation of other brain areas, such as the hippocampus, FG and STG (for review, see chapter 1 and Dolan, 2002; Sander et al., 2003). The hypoactive amygdala model of ASD sees a break-down in this modulation as a primary cause of social-perceptual impairment in ASD (Grelotti et al., 2002; Schultz et al., 2000b; Schultz, 2005). For example, Schultz et al. (2005) suggest that many of the face processing deficits in ASD might be traced back to a failure of the amygdala to influence activity in the FG.

The neuromodulatory role of the amygdala, in response to salient events, has been neatly demonstrated via the phenomenon of the emotional modulation of the attentional blink (Anderson and Phelps, 2001). When two masked targets (known as T1 and T2) are presented within approximately 500 msecs of each other, subjects are often unable to report the second of the two targets accurately, even though the first has been reported correctly (Raymond et al., 1992). Allocating attention to T1 is thought to leave less attention available for T2, rendering T2 vulnerable to decay or substitution – hence the transient ‘blink’ in attention (for review, see Shapiro et al., 1997). However, the size of the attentional blink is greatly attenuated if T2 stimuli are emotionally charged (Anderson, 2005; Anderson and Phelps, 2001; Arend and Botella, 2002; Ogawa and Suzuki, 2004). Affective modulation of the attentional blink is most evident when T1 and T2 are close together, which is when attentional resources are most occupied with the processing of the preceding T1. Further experiments have shown that it is the arousal quality of the
emotional stimuli, rather than their valence, that enhances the ability of T2 to be detected (Anderson, 2005).

Consistent with its role in enhancing perception for emotional events, amygdala integrity has been shown to be crucial for emotional modulation of the attentional blink. Patients with amygdala damage show much reduced perceptual benefit for arousing T2 stimuli, despite unaffected comprehension of their affective quality (Anderson and Phelps, 2001). These deficits are most marked when T2 occurs shortly after T1 – i.e. when attention is most stretched. The emotional modulation of the attentional blink therefore provides a behavioural paradigm for investigating the integrity of the amygdala in general and, specifically, the amygdala’s ability to modulate processing in other brain regions in response to emotionally salient events.

The hypo-active amygdala model of ASD proposes that the amygdala fails to flag emotionally or socially relevant stimuli as salient and therefore fails to modulate other areas of the brain in order to enhance perception of that stimulus. Therefore, this model predicts that, like patients with amygdala damage, individuals with an ASD will:

a) show reduced enhancement of perception for emotionally arousing events in an attentional blink paradigm, compared to matched controls

b) that this difference should be most obvious when the lag between T1 and T2 is short – i.e. when attention is most stretched and normal controls show the greatest perceptual benefit for arousing stimuli

c) that these effects can not be attributed to differences in how arousing the stimuli are perceived by the two groups
Experiment 1

Methods

Participants

17 adults with a diagnosis of AS and 17 gender matched controls took part in the study. Age and IQ were matched as closely as possible (see table 31). AS diagnosis was confirmed via the ADOS and AQ. On this occasion, AQs were not taken for the control group.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Gender</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
<th>Full IQ</th>
<th>AQ score</th>
<th>ADOS Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>34.2</td>
<td>15 M</td>
<td>109.4</td>
<td>112.1</td>
<td>112.9</td>
<td>34.9</td>
<td>8 Autism</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(11.99)</td>
<td>2 F</td>
<td>(14.27)</td>
<td>(15.25)</td>
<td>(13.99)</td>
<td>(9.0)</td>
<td>9 Autistic spectrum</td>
</tr>
<tr>
<td>Controls</td>
<td>32.3</td>
<td>15 M</td>
<td>108.7</td>
<td>108.7</td>
<td>109.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(13.26)</td>
<td>2 F</td>
<td>(10.99)</td>
<td>(8.18)</td>
<td>(8.57)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 31. Characteristics of the groups who took part in the attentional blink experiments.

The experiment was in two parts: the first was the attentional blink experiment itself; the second, which took place at least one week later, measured subjects' arousal response to the T2 words, both via self-report and SCR recording. Details of the design and procedure for these two parts to the experiment are given separately below.
Emotional modulation of the attentional blink experiment

The first target stimuli (T1) were 38 neutral words. The second target stimuli (T2) consisted of 19 negative-arousing words (e.g. rape, bastard) and 19 neutral words (e.g. basin, sparrow). The arousing words were the same as those used in previous experiments, where they have been shown to produce a large attenuation of the attentional blink in normal subjects (Anderson, 2005; Anderson and Phelps, 2001). The neutral words were taken from the ANEW ‘Balanced Affective Word List’ (http://www.sci.sdsu.edu/CAL/wordlist/) and were chosen to have low ratings for arousal.

The negative and neutral word lists were matched for average word length and semantic relatedness. Distractor stimuli were 326 neutral words, again taken from the ANEW list, matched in length with the target words.

Each trial consisted of 15 words – 2 targets and 13 distractors (see figure 27). T1 and T2 were designated as targets by appearing in black, whereas the distractor words appeared in a random selection of 4 colours (yellow, red, green and blue; the same colour was not allowed to appear twice in a row). Each item in the stream was presented for 120 msecs and was immediately followed by the subsequent item. A random number of distractors (between 3 and 6) appeared before T1. T2 was presented at one of four possible times after T1 – 120 msecs (no intervening items), 360 msecs (two intervening items), 600 msecs (four intervening items) or 840 msecs (six intervening items). The shorter two of these four T1-T2 lags are within the time window during which T2 is susceptible to an attentional blink, the later two are beyond this window (Shapiro et al., 1997). There were 19 trials for each factor combination of lag (1-4) and word type (neutral versus arousing), resulting in 152 trials. The subjects' task was to monitor the stream of words and to report the identity of the two black target words (T1 and T2) by writing them down at the end of
the stimulus sequence. Trials where subjects failed to correctly identify T1 were excluded from analysis (this occurred on < 5% of cases). The dependent measure was the number of T2 stimuli correctly identified.

Words were presented in Geneva font, 30 point type, on a uniform light grey background. Viewing distance was approximately 40 cm.

Figure 27. Diagram of the attentional blink task.

Words were briefly presented sequentially in an identical central location and observers were instructed to ignore the coloured words (distractors) and indicate the identity of two target words appearing in black. The temporal lag between the first (T1) and second target (T2) was varied. We used two short lags (120 ms or 360 ms), during which T2 is susceptible to the attentional blink, and two long lags (600 ms and 840 ms) at which T2 is less susceptible to the attentional blink. The dependent measure was the percentage of T2s correctly identified.

Arousal measurements

To assess perceived arousal to the T2 stimuli, subjects viewed all 38 T2 words (19 neutral and 19 arousing) sequentially on a computer screen (Geneva font, 30 point, viewing distance approximately 40 cm), whilst their SCRs were recorded. Each word was shown
for 4.5 seconds. During this time subjects were instructed to read the word silently to themselves but to remain still. Following the presentation of each word, there was a blank screen for 0.5 seconds followed by the question, “How emotionally arousing did you find that word?” This was the cue for subjects to rate the arousal quality of the word on a scale of 1 – 5 via a keyboard press. On this scale, ‘1’ represented, ‘not at all arousing’ and ‘5’ represented, ‘very arousing’. There was an unlimited time to answer. To allow the skin conductance trace to return to baseline, there was a gap of at least 16 seconds between words.

SCRs were recorded and analysed in accordance with the method outlined in chapter 2. Briefly, a SCR was considered to be in response to a word if it began between 1 and 3 seconds post stimulus onset (Dawson et al., 2000). Only the first response occurring in this time window was analysed. The amplitude of each SCR was recorded and the mean SCR amplitude was calculated for each word type (neutral or arousing), separately for each group.

Results

Self-reported arousal in response to the words

Table 32 summarises how the groups rated the words in terms of emotional arousal. These data were analysed using an ANOVA. There was a highly significant effect of word type, $F(1,32) = 70.5, p < .001$, suggesting that the

<table>
<thead>
<tr>
<th>Word Type</th>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral Words</td>
<td>Controls</td>
<td>2.0</td>
<td>.73</td>
</tr>
<tr>
<td></td>
<td>AS</td>
<td>1.8</td>
<td>.63</td>
</tr>
<tr>
<td>Arousing Words</td>
<td>Controls</td>
<td>3.6</td>
<td>.78</td>
</tr>
<tr>
<td></td>
<td>AS</td>
<td>3.3</td>
<td>1.16</td>
</tr>
</tbody>
</table>

Table 32. Summary of how the two groups rated the arousal quality of T2 words. Subjects rated each word on a scale of 1 to 5, where 1 was ‘not at all arousing’ and 5 was ‘very arousing’.
participants did indeed find the arousing words more emotionally salient than the neutral words. However, there was no effect of group, $F(1,32) = 1.6, p = .22$ and no significant interaction, $F(1,32) = .09, p = .76$, suggesting that the two groups were comparable in terms of how emotionally arousing they found the words.

**Autonomic measure of arousal in response to the words**

Table 33 shows the mean amplitude of the SCRs made to the words. These data were normalized via a square root transformation and then analysed via ANOVA. There were significant effects of word type, $F(1,32) = 49.8, p < .001$, and group, $F(1,32) = 4.5, p = .04$.

<table>
<thead>
<tr>
<th>Word Type</th>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral Words</td>
<td>Controls</td>
<td>.12</td>
<td>.107</td>
</tr>
<tr>
<td></td>
<td>AS</td>
<td>.22</td>
<td>.082</td>
</tr>
<tr>
<td>Arousing Words</td>
<td>Controls</td>
<td>.29</td>
<td>.148</td>
</tr>
<tr>
<td></td>
<td>AS</td>
<td>.35</td>
<td>.135</td>
</tr>
</tbody>
</table>

Table 33: Mean SCR magnitudes to the words, split by group. Data are in $\sqrt{\mu}$ Siemens.

Importantly, however, there was no evidence of a group x word type interaction, $F(1,32) = .73, p = .4$. This suggests that, while the AS subjects had a higher autonomic reaction to the words in general, the groups were comparable in terms of how they differentiated between the neutral and arousing words.

**Emotional modulation of the attentional blink**

Figure 28 summarises the results of the attentional blink experiment. These data were entered into an ANOVA with word type and lag as repeated measures variables and group as a between measures variable.
As predicted, there were highly significant effects of lag, $F(3, 96) = 30.9$, $p < .001$, and word type, $F(1, 32) = 23.2$, $p < .001$. Post-hoc comparisons show that significantly more T2 words were identified for lags 3 and 4 compared to both lags 1 and 2 (all $p < .001$, Bonferroni corrected). Subjects correctly identified more arousing than neutral T2s at every lag (all $t > 3.1$, all $p < .012$, Bonferroni corrected). However, there was a significant word type x lag interaction - $F(1, 32) = 23.2$, $p < .001$, reflecting the fact that the effect of word type was stronger at earlier lags (mean enhancing effect of arousing words for each lag: 120 msecs = 16%, 360 msecs = 9%, 600 msecs = 5% and 840 msecs = 6%). In summary, arousing T2s were more easily identified and this effect was stronger at shorter T1-T2 lags when attention was most stretched.
Contrary to predictions, there was no word type x group interaction, $F(1,32) = 1.7, p = .2$, i.e. there was no evidence that AS subjects showed less enhancement of perception for the arousing words in general. However, there was a significant word type x lag x group interaction – $F(3,96) = 5.2, p = .002$. To investigate this further, the difference in the percentage of correctly identified arousing, compared to neutral, T2s was calculated separately for each group at each lag. As table 34 (and figure 28) shows, at Lag 1 (120 msecs) controls demonstrated a greater perceptual benefit for arousing words than did AS subjects – $t(32) = 2.5, p = .018$ uncorrected, .072 Bonferroni corrected. Such differences were not evident at longer lags – all $t < .71, all p > .48$.

For the AS subjects, table 35 shows the correlations between the size of the emotional modulation of the attentional blink at lag 1 and both severity of autistic symptoms and fear recognition score.

<table>
<thead>
<tr>
<th>ADOS Com</th>
<th>ADOS RSI</th>
<th>ADOS Total</th>
<th>AQ</th>
<th>Fear recognition score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r$</td>
<td>-.28</td>
<td>-.31</td>
<td>-.32</td>
<td>-.14</td>
</tr>
<tr>
<td>$p$</td>
<td>.36</td>
<td>.31</td>
<td>.30</td>
<td>.60</td>
</tr>
</tbody>
</table>

Table 35. Correlations between the size of the effect of arousal on T2 identification (i.e. the difference between the percentage of arousing T2 and neutral T2 correctly identified) and the severity of autistic symptoms and fear recognition score.

ADOS = autism diagnostic observational schedule. ADOS Com = communication sub-scale of the ADOS. ADOS RSI = reciprocal social interaction subscale of the ADOS. AQ = autistic spectrum quotient.
Proportion of subjects showing no advantage for arousing T2s, or showing less advantage than SM

An alternative way to analyse these data is to ask what proportion of each group showed absolutely no advantage for arousing versus neutral T2 (i.e. their percentage of correct arousing T2 stimuli minus their percentage of correct neutral T2 stimuli was \( < 0 \), averaged across all T1-T2 lags). 5 of 17 AS subjects (29% of sample) fulfilled this criteria, compared to 1 of 17 controls (6% of sample), a difference which showed a trend towards significance: \( \chi^2 = 3.3, p = .08 \).

Using an almost identical paradigm to the one used here, Anderson and Phelps (2001) report that a patient with bilateral amygdala damage showed a 2% advantage for arousing versus neutral T2 stimuli at short T1-T2 lags (compared to 22.6% for controls). In the current study, 7 of 17 AS subjects (41% of sample) showed \( \leq 2\% \) advantage for arousing versus neutral T2s, compared to 1 of 7 controls (6% of sample), a difference which is significant: \( \chi^2 = 5.9, p = .02 \).

Within the AS group, there were no significant differences in perceived arousal of the T2 stimuli between those who showed no perceptual benefit for them (or less perceptual benefit than SM) compared to those who did show such an advantage (see tables 36 and 37). Neither were there differences in IQ or severity of autistic symptoms between these groups.
### Table 36.
Comparing those AS subjects who show no perceptual benefit for arousing T2s to those that do. There were no significant differences – all \( t < .91 \), all \( p > .37 \)

### Table 37.
Comparing those AS subjects who show less perceptual benefit for arousing T2 than SM to those who show more. Again, there were no significant differences – all \( t < 1.4 \), all \( p > .18 \)

'Self-reported arousal difference' is the difference between how arousing the subjects rated the T2 arousing words compared to the T2 neutral words. 'SCR difference' is the difference in mean SCR amplitude to these stimuli types.

**Experiment 2**

In experiment 1, AS subjects appeared to show reduced emotional modulation of the attentional blink at the earliest time lag (when attention was most stretched). However, rather than reflecting an impairment specifically in affective modulation of perception, this difference may be due to a disruption of a more global process, which effects any type of modulation of perceptual encoding. To investigate this possibility, I conducted a second experiment where the salience of the T2 stimuli was altered in terms of visual-perceptual, rather than emotional, attributes.
Methods

Participants
The same subjects who took part in experiment 1 took part in experiment 2.

Attentional blink control experiment
The design and procedure was largely the same as experiment 1. However, on this occasion all T2 words were neutral in content and their salience was adjusted by altering their brightness. Higher salience T2s were jet black (R,G,B channels all 100%), which meant that they stood out clearly against the grey background and multi-coloured distractors. Lower salience T2s were dark grey (R,G,B channels all 75%), with the result that they stood out less clearly. T1 stimuli were mid-way between the two types of T2 in terms of brightness (R,G,B channels all 87.5%).

Results
Figure 29 summarises the results of the control attentional blink experiment. Again, these data were entered into an ANOVA, with lag and T2 salience as repeated measures variables and group as a between measures variable.
As before, there were main effects of lag,
$F(3,96) = 59.8, p < .001$, and T2 salience,
$F(1,32) = 33.5, p < .001$, as well as a lag x
dsalience interaction, $F(3,96) = 2.7, p = .04$.
Although it is not clear in figure 29, this
interaction again seems to be due to T2
salience having a greater effect at shorter
lags, when attention in most stretched (see
table 38).

<table>
<thead>
<tr>
<th>T1-T2 Lag</th>
<th>Mean (%)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 msec</td>
<td>15.2</td>
<td>15.47</td>
</tr>
<tr>
<td>360 msec</td>
<td>10.8</td>
<td>17.41</td>
</tr>
<tr>
<td>600 msec</td>
<td>8.0</td>
<td>18.82</td>
</tr>
<tr>
<td>840 msec</td>
<td>5.5</td>
<td>11.54</td>
</tr>
</tbody>
</table>

Table 38. The perceptual benefit for high-salience
T2s at different T1-T2 lags.

There was no main effect of group, $F(1,32) = 2.4, p = .13$ and, importantly, no lag x
salience, $F(1,32) = .22, p = .64$, or lag x salience x group interaction, $F(3,96) = .38, p =$
This suggests that the effect of manipulating T2 salience was the same for both groups at each lag.

**Discussion**

There was no evidence that AS subjects showed a general reduction in perceptual benefit for emotionally arousing stimuli compared to controls – i.e. in experiment 1 there was no group x word type interaction. However, at the shortest T1-T2 lag, when attentional resources were most stretched, controls showed a much greater perceptual enhancement for arousing T2s than did AS subjects. In this regard the AS subjects are reminiscent of SM, whose reduced perceptual benefit for arousing words was most evident at the shortest T1-T2 lag (Anderson and Phelps, 2001). In addition, a greater proportion of AS subjects showed no, or little, perceptual advantage for arousing T2s: - 29% of AS subjects showed absolutely no advantage, while 41% showed less advantage than a patient with bilateral amygdala damage in a similar paradigm (Anderson and Phelps, 2001). For controls, the figure was 6% in both cases.

Together, the data therefore offer partial support for the predictions made by the hypo-active amygdala model, suggesting that the efficacy of the amygdala’s perceptual enhancement system may be reduced in AS and in some subjects may be as ineffective as it is in those with bilateral amygdala lesion.

The hypo-active model cites a failure in the amygdala to perform its usual perception-enhancing role as a primary cause of the social-perceptual problems in the disorder (Klin et al., 2005; Schultz et al., 2000b). The fact that the AS subjects who showed the largest emotional modulation of the attentional blink tended to have the best fear recognition
ability offers some support for this position. However, the correlation was only marginally significant and so should be interpreted with caution.

Control experiments showed that these differences could not be explained by differences in the perceived arousal level of the T2 stimuli, measured by both self-report and skin conductance. In addition, a control attentional blink experiment in which T2 salience was modulated visuo-perceptually rather than emotionally found no differences between the two groups. However, on this occasion neither group showed the large benefit for the high salience T2s during the shortest T1-T2 lag which was evident for the control group in experiment 1. This highlights the special effect of emotion for the control but not the AS subjects. In fact, the shape of the graph is very similar for the AS group in both experiment 1 and 2, perhaps indicating that the subjects treated the stimuli in much the same manner.

The finding of some, albeit limited, support for the hypo-active amygdala model, at least in some subjects, suggests the interesting possibility that both the hypo- and hyper-active amygdala models might be in operation but in different populations of AS individuals. Hirstein et al. (2001) proposed something similar when they found evidence of two distinct groups of autistic children: those who experienced hyper-arousal of the autonomic system (the majority) and those who experienced hypo-arousal. Unfortunately, there was very little cross-over between the AS subjects who took part in the attentional blink experiments and the group who took part in the earlier experiments: therefore it is not possible at this time to directly compare results from the two sets of experiments. The possible existence of two distinct groups of AS individuals is discussed in greater depth in the next chapter, where some suggestions are made for possible experiments to investigate the issue.
One caveat is that T2 stimuli were emotional but they were not social. It is possible that the AS subjects would have shown less perceptual enhancement for strictly social stimuli (faces perhaps) than emotional words. However, with social stimuli the experiment may have been confounded by the subjects' abnormal fixation patterns towards the stimuli. Also, using emotional words provided a stronger test of the neurological predictions made by the hypo-active model – total failure of amygdala to modulate other brain areas in response to any salient stimuli. Still, it is possible that the amygdala's failure to enhance perception is stimulus type dependent – social stimuli may have an effect where generally emotional stimuli do not.
Chapter 7 - General Discussion

Summary of findings

The amygdala has long been associated with emotional processing but recently theorists have suggested it may form an important component in a social cognitive module, subserving behaviour in response to conspecifics (Brothers, 1990). This thesis investigated the role of the amygdala in social cognition by examining variability in social-perceptual abilities in the normal population and via experiments with AS individuals, whose social cognitive impairments are thought of as a core component of their disorder (American Psychiatry Association, 1994).

As a theoretical background, these experiments were informed by models where the amygdala is seen as a ‘salience’ detector, functioning to enhance the perception of, or memory for, an emotionally or socially relevant event via modulation of other brain areas (Dolan, 2002; Sander et al., 2003). In the hypo-active amygdala model of ASD, failure in this system results in a lack of attention towards socially important stimuli (Grelotti et al., 2002; Schultz et al., 2000b; Schultz, 2005). In the hyper-active amygdala model, stimuli are actively avoided to prevent aversive over-arousal (Dalton et al., 2005; Nacewicz et al., in press). In either case, failure to attend to social stimuli is thought to result in social cognitive impairment. This could happen both in real-time, simply through failing to spot the socially relevant aspects of the environment, and developmentally, because prolonged under-exposure to social stimuli is thought to result in under-development of social-perceptual areas, such as the FG and STS (Schultz, 2005).
In my experiments with males from the normal population, I found that a significant minority had a marked deficit in their ability to recognise fearful expressions. This impairment was of a level akin to patients with bilateral amygdala damage (e.g. Calder et al., 1996). In addition, social cognitive deficits in the low fear scoring group (LFS) extended to encompass theory of mind abilities. Using fMRI, I found that LFS showed reduced activation of diffuse areas of the social brain, including the amygdala, in response to a socially relevant stimulus. There was also reduced functional connectivity, in LFS, between the amygdala and the anterior STG and MPFC – areas known for their involvement in theory of mind processing. These data suggested provocative conclusions. Firstly, that variability in the functional capabilities of the amygdala and other areas of the social brain might underlie important individual differences in social cognitive skills within the healthy male population. Secondly, and more specifically, that failure of the amygdala to flag social stimuli as salient and to then modulate activity in other brain regions, where fine grained perception of these stimuli takes place, might be the mechanism by which differences in social cognitive ability arise.

However, eyetracking experiments showed that LFS do not fixate on the eyes as much as NFS. While this is reminiscent of patient SM (Adolphs et al., 2005), again suggesting altered amygdala function in LFS, it brings the interpretation of the fMRI results into question. Were the brains of the LFS and NFS participants reacting differently to the same visual input or were they looking at the stimuli differently, therefore receiving different visual input? More experiments are required to answer this question but a link between poor fear recognition and the amygdala in LFS remains a possibility.

I hypothesised that, since LFS had problems with social-perception in the laboratory, they may have difficulties in social interaction and communication in their day-to-day lives.
However, LFS do not experience more autistic-like traits than the general population, as measured by the AQ (Baron-Cohen et al., 2001b), even when considering only those subscales of the AQ that specifically ask about behaviour in social situations. LFS subjects do, however, rate themselves as more anxious, more neurotic and more socially phobic than NFS. This raises the possibility that anxiety, low eye fixation and poor fear recognition may be linked in LFS: affected individuals may find eyes aversive and so avoid them, echoing the hyper-active amygdala model of ASD. As discussed in chapter 3, this is only one of a number of possibilities for explaining the LFS findings and more research is required before definitive conclusions may be drawn. Some suggestions for future work were given in chapter 3 but will be discussed again in a later section of this chapter.

I began my experiments with AS subjects in the same way as I did for the normal population – by examining fear recognition ability. I found evidence of an impairment in identifying fearful faces, which also existed for sad expressions. Whether such a deficit exists has been a controversial question in ASD research but, I argue in chapter 4, my data add to a growing consensus for a fear recognition impairment amongst adults with high-functioning autism or AS. However, there was a great deal of variability in the AS group: some subjects performed normally or better than average, while others were severely impaired. The cause of the fear recognition deficit and of its variable manifestation may lie in differences in the way AS subjects fixate faces. Like SM and LFS, I found that, as a group, subjects with AS spent less time fixating the eyes compared to age, gender and IQ matched controls and that there was a significant correlation between the percentage of fixations to the eyes and fear recognition score.
I next investigated the possible cause for the reduced eye fixation in AS, taking direction from the hyper- and hypo-active amygdala models of ASD. I found that both high social anxiety and high autonomic responses to the eyes were associated with less time spent fixating eyes and poorer fear recognition. This was consistent with the theory that some AS subjects actively avoid eyes to prevent over-arousal. I linked this to the amygdala with a VBM study: grey matter volume in the left amygdala correlated with low social anxiety, low autonomic response to the eyes, more time spent fixating the eyes and high fear recognition. This replicated and extended work by Nacewicz et al. (in press), who suggest that smaller amygdala volumes in adult AS subjects who fixate the eyes the least are caused by a hyper-activity induced atrophy. As a whole, the findings presented in chapters 4 and 5 generally support the hyper-active amygdala model of ASD, whereby high allostatic load is thought to lead to both amygdala atrophy and avoidance of anxiety-inducing social stimuli, leading to an impairment in social cognition.

In my final study, I used the emotional modulation of the attentional blink to test the hypothesis, made by the hypo-active amygdala model, that the AS amygdala fails to enhance perception for emotionally salient events. I found that AS subjects did show a perceptual benefit for arousing stimuli in general, but that the size of this benefit was reduced compared to controls when attention was most stretched. In addition, a significantly greater number of AS than control subjects showed little or no perceptual benefit for the arousing events. This is consistent with a breakdown in the amygdala perception-enhancing system and provides partial support for the hypo-active amygdala model in at least a sub-set of AS subjects.

Together, these results provide support for a general route to social cognitive impairment, which has the failure to attend social stimuli as its basis. There may be a number of root
causes for the inattention to social stimuli, but the hyper- and hypo-amygdala models of ASD provide two plausible, evidence based possibilities. In the remainder of this chapter, the details of this general route to social cognitive impairment and its implications for ASD and other disorders of social cognition will be discussed. Following this, some unanswered questions and ambiguities will be considered, as will be the limitations of the current work and the field in general. Finally, suggestions will be given for taking the project forward.

**Implications and further discussion**

**A general ‘route’ to social cognitive impairment?**

The major implication of my findings is that failure to attend to the socially relevant parts of the environment could be a common route\(^\text{19}\) to social cognitive or, at least, social perceptual deficits in a wide variety of populations (see figure 30). For example, in subjects with LFS, ASD and psychopathy (Dadds et al., in press) there is evidence of both social cognitive deficits, including poor fear recognition, and a failure to fixate the eyes.

\(^{19}\) I call this a ‘route’ because it is likely to be only one of a number of possible pathways to social cognitive impairment. Multiple routes could be in operation in the same individual or group of individuals and may interact, leading to profound and variable differences in social cognitive abilities in different psychiatric groups.
Under-development of social-perceptual processing in regions such as the FG and STG.

Social-perceptual deficits

Under-development of social-perceptual processing in regions such as the FG and STG.

Hypo-active model
The amygdala is under-reactive to social stimuli, therefore it fails to flag them as significant. As a result, social stimuli are ignored.

Hyper-active model
The amygdala is over-reactive to social stimuli, producing over-arousal, which is aversive. As a result the arousal producing stimuli are avoided.

Alternative hyper-active model
The amygdala is constantly over-reactive, rendering it ineffective at discerning between significant and non-significant stimuli. As a result, social stimuli are often missed.

Other possible aetiologies

Lack of 'scaffolding' necessary to understand non-verbal communication

Deficits in social-cognitive skills such as ToM

Over time leads to...

Social-perceptual deficits

Impairment in day to day social functioning

Impairment in executive function

Weak central coherence

Low IQ

Figure 30. Routes to social impairment with 'inattention to social stimuli' as their basis.
The same may be true of Turner’s syndrome, although the eyetracking experiments have yet to be completed.

One mechanism whereby inattention to socially relevant stimuli may exert its deleterious effect on social perception is via development. Some neurofunctional models of ASD propose that failure to orient to social stimuli, if it occurs early in life, can lead to under-development of brain areas such as the FG and STS (Schultz et al., 2000b; Schultz, 2005). Since these areas are thought necessary for computations which provide the ‘scaffolding’ required to understand the barrage of non-verbal communications that occur during social interactions, under-development of these circuits could result in a wide-range of social-cognitive deficits (Schultz, 2005). As well as applying to ASD, it is possible that this model may explain some of the social cognitive deficits seen in other populations, such as LFS and Turner’s syndrome.

Alternatively, however, failure to attend stimuli such as the eyes could cause problems of social perception, such as poor fear recognition, in real-time alone. One could envisage, for example, an adult who has a fully developed FG and STS but who, perhaps because of amygdala damage, stops orienting towards socially relevant stimuli. Social perceptual deficits would ensue simply because the brain does not receive the necessary input, not because the brain is incapable of processing that input correctly if it does receive it. This is perhaps the case for SM, whose amygdala lesion appears to have led to a failure to fixate the eyes and a corresponding fear recognition deficit. However, when she is encouraged to look at the eyes her fear recognition score improves dramatically, suggesting that her brain is able to process the stimuli correctly if it receives the necessary visual input.
In contrast, my AS subjects' fear scores did not improve dramatically when they were made to look at the eyes, suggesting that they were not able to correctly process the stimuli even when directed towards it. This perhaps indicates that failure to attend the eyes has existed from early in life in these subjects, therefore supporting the developmental account advocated by the hyper- and hypo-active models. Consistent with this is the research showing that reduced orienting towards faces exists at a young age in children who are later diagnosed with an ASD (Osterling and Dawson, 1994).

In my LFS sample however, I have not yet investigated the change in fear scores when the subjects are instructed to fixate the eyes, so the situation is less clear. For the future it will be important, as it will be whenever the ‘lack of social attention’ route to social-cognitive impairment is suspected for a particular population, to ascertain to what extent their particular deficits are developmental in origin and to what extent they can be explained by inattention to social stimuli in real-time alone.

So far in this section I have discussed how failure to pay attention to socially relevant parts of the environment could be a common route to social cognitive impairment in various populations. What I have not yet discussed are the potential causes of this inattention. There may be many possibilities, but this thesis explicitly investigated two which other authors have suggested specifically for ASD. These were the hyper- and hypo-active amygdala models of ASD and they will be discussed in the next section.
The hyper- versus the hypo-active amygdala models of ASD and their possible role in other disorders of social cognition

These models offer two different possible causes of inattention to social stimuli in ASD. The hyper-active amygdala model suggests that affected individuals find social stimuli over-arousing and hence aversive. Such stimuli are therefore actively avoided. Neurofunctionally, this model predicts heightened amygdala responsiveness to relevant stimuli (so long as attention is directed towards those stimuli); neuroanatomically it predicts an initial outgrowth (in childhood) and later atrophy (in adulthood) of amygdala neurons (see Nacewicz et al. in press). The hyper-active model has its roots in the work of Ilutt and Ounsted (1969), but the major proponents of its modern incarnation are Richard Davidson, David Amaral and colleagues (Amaral and Corbett, 2002; Dalton et al., 2005; Nacewicz et al., in press).

According to the hypo-active model, the amygdala in ASD fails to flag socially relevant stimuli as salient. The result is a lack of social interest; hence social stimuli are ignored rather than avoided. Neurofunctionally, this model predicts reduced amygdala responsiveness to relevant stimuli; neuroanatomically, no specific predictions are made. Conceptually, this kind of theory could be traced back to Kanner (1943), who suggested that reduced ‘affective contact’ was at the heart of autism. However, its most vocal supporters in recent years have been Bob Schultz and colleagues (Grelotti et al., 2002; Schultz et al., 2000b; Schultz, 2005).

As a whole, the experiments in chapters 4 and 5 of this thesis supported predictions made from the hyper-active amygdala model: both high social anxiety and high autonomic response to eyes predicted low eye fixation and poor fear recognition ability. In addition,
each of these variables was associated with smaller amygdala volume. There are some
caveats, which will be discussed below, but the data suggest that a process along the lines
of that outlined by the hyper-active model is indeed leading to social-perceptual
impairment in some individuals with AS.

The first caveat is that only one of the autonomic measures (the number of SCRs made to
eyes compared to mouths) predicted low eye fixation and poor fear recognition; the other
(summed amplitude of SCRs to eyes compared to mouths) showed no correlation. A
second issue is that the model specifically predicts heightened amygdala activity but a
direct measure of this has not been taken. Finally, the attentional blink experiment
presented in chapter 6 provides some, albeit limited, support for the hypo-active model, at
least in some subjects. As discussed in detail in chapter 5, a crucial step in resolving these
issues will be to conduct an experiment where amygdala activity is measured, by fMRI,
while the direction of the subjects’ fixation (either to the eyes or the mouth) is carefully
manipulated. Conducting this experiment is the vital next step in this programme of
research (see ‘future directions’ section below).

The fact that there is some support for the hypo-active amygdala model, at least in some
subjects, suggests the interesting possibility that both models may be operating but in
different populations of AS individuals. At least two other groups have made a similar
proposal before. For example, Hirstein et al. (2001) conducted experiments measuring
SCR activity of autistic children while they looked at faces and during everyday
behaviours and concluded that there are two types of autistic child: those who experience
hyper-active sympathetic activity (the majority) and those who experience hypo-activity
(a small percentage). Dalton et al. (2005) suggest a similar hypothesis when they found
the majority of autistic subjects in their sample exhibited hyper-activity of the amygdala, while a small percentage showed hypo-activity compared to controls.

However, the Hirstein et al. (2001) study has a number of methodological problems, the case and control groups are wildly unmatched for example, and to my knowledge the study has not been replicated. Furthermore, Dalton et al. (2005) mention the possible existence of a hypo- and a hyper-active group only as an afterthought in their discussion - they do not formally present data on the issue. Therefore, these studies are far from definitive. Given the potential theoretical importance of the issue, repeating these studies in a more controlled and transparent manner should be a priority. A large scale study involving many subjects would be necessary to gain a true sense of the relative size of the hyper- and hypo-active groups, if both do indeed exist. SCRs and/or amygdala activity should be monitored at rest and in response to a number of controlled social and non-social stimuli or events. Control groups should be carefully matched and care should be taken over potential confounds of SCR measurement, such as the time of day that the recordings are taken and the temperature of the room whilst this is being done (Dawson et al., 2000). As well as a ‘normal’ control group it will also be necessary to have groups that suffer from anxiety and social phobia, but not autism. This will allow an investigation of the extent to which autonomic peculiarities are independent of co-morbid anxiety in ASD.

A final caveat is that there are a number of AS individuals who showed no evidence of either model. For example, some subjects spent a normal amount of time fixating the eyes, had normal fear recognition ability, normal emotional modulation of the attentional blink, a normal autonomic response to eyes versus mouths and a normal amygdala volume – yet these same subjects were severely impaired in terms of reciprocal social interaction and
communication, according to the ADOS and AQ. There are at least two explanations for this:

1) the processes proposed by the two models (e.g. inattention to social stimuli etc) are not necessary to cause day to day social impairment in AS

2) the processes proposed by the two models are necessary and are causing day to day social impairment in these individuals but they are employing compensatory strategies, which mean that evidence for either model is not apparent using our laboratory tests

The first of these explanations is compatible with the idea that inattention to social stimuli is one of a number of possible routes to social cognitive impairment in ASD and other disorders. Other deficits in such things as executive function and central coherence may be involved in causing day to day social impairment in these individuals. It is also compatible with the idea of heterogeneity in ASD, with the possibility of there being multiple sub-types within the disorder (e.g. Hrdlicka et al., 2005; Klin et al., 2005; Verte et al., 2006b). To investigate explanation (1) it would be useful to gain a thorough profile of the individuals who show no evidence for either the hyper- or hypo-active amygdala models. This should include tests of executive function and weak central coherence as well as an attempt to characterise the nature of their day to day social impairment, with a view to comparing this to other individuals who do show evidence for one of the models.

Explanation (2) has some plausibility as some studies of face processing in ASD have shown that, while subjects may achieve a higher than expected result on a given task, they may be doing so in an atypical fashion (e.g. Pierce et al., 2001; Schultz et al., 2000a). This highlights the potential importance of focussing on the processes used by individuals when completing an experimental task, and not only on the results obtained (Volkmar et
al., 2004). When it comes to fear recognition, it is possible that an individual may have constructed an alternative strategy to recognise the emotion. The *Bubbles* task (Gosselin and Schyns, 2001; Smith et al., 2005) would be an ideal method for investigating this.

With regard to eye fixation, people with an ASD are often encouraged to fixate the eyes by parents, teachers etc. It is possible that some of the subjects with a high eye fixation percentage may be making an unnaturally conscious effort to fixate the eyes, resisting the urge to look away from them. Interviews or questionnaires may be a suitable method for investigating this. However, despite these possibilities, the existence of compensatory strategies could not explain all instances where some individuals do not fit either the hyper- or hypo-active model – it is difficult to see how such strategies could affect the autonomic or neuroanatomical data, for example. It therefore seems likely that other routes to social cognitive impairment are in operation in some individuals. This makes it even more important to profile the individuals who show no evidence of the models and to examine other possible routes to social cognitive impairment in ASD.

So far in this section I have talked mainly about the hyper- and hypo-active models in terms of ASD. However, if inattention to social stimuli is a general route to social cognitive impairment, then processes similar to those proposed in the hyper- and hypo-active models might be the cause of social deficits in other populations, such as LFS, psychopathy or Turner’s syndrome (see figure 30). The heightened anxiety in LFS, for example, perhaps hints at a hyper-active type model, although of course much more work needs to be done to investigate this further. Similarly, there have been suggestions of increased anxiety and heightened amygdala and autonomic responsiveness in Turner’s syndrome (Keysor et al., 2002; Skuse et al., 2005), although these have not been linked specifically to social cognitive impairment. More work clearly needs to be done, but it
would be interesting to see how lessons from ASD might be applied to other disorders of social cognition.

The hyper-active model – unresolved issues

As a whole, my data offers most support for the hyper-active amygdala model in ASD and hints at a similar mechanism in LFS. However, there are a number of ambiguities and unresolved issues with this theory, which will be discussed below.

Amygdala hyper-activity, anxiety and social cognitive impairment in ASD

The nature of the relationship between amygdala hyper-activity, anxiety and social cognitive impairment under the hyper-active model requires elucidation. One problem is that the model supposes that anxiety results in avoidance of anxiety-inducing stimuli in ASD, whereas there is a large literature showing that anxious and socially anxious individuals from the normal population are hyper-vigilant for such stimuli. This was discussed at some length in chapter 5, where I suggested two possible explanations for the apparent discrepancy:

1) there may be an interaction between autistic symptoms and anxiety – i.e. people with an ASD might react to and cope with their anxiousness in a different way to non-ASD individuals. Consistent with this is the suggestion by Pfeiffer et al. (2005) that anxiety produces ‘sensory defensiveness’ in ASD, rather than hyper-vigilance

2) the discrepancy may be explained by the actual levels of anxiety / social anxiety involved in the different studies. The levels experienced by my AS sample were generally higher than the ‘high anxiety’ groups used in the studies of the normal
population, and the 'low anxiety' groups in these studies were considerably less anxious than my normal control group. I suggested that the relationship between anxiety and vigilance towards social stimuli might follow an inverted U shape, where medium-high anxiety corresponds to hyper-vigilance but very high or low anxiety corresponds to hypo-vigilance.

It will be important to investigate these possibilities in order to refine the hyper-active amygdala model.

Another unresolved issue, which is potentially a deeper problem for the hyper-active model, concerns the causes of anxiety / social anxiety and amygdala hyper-activity in ASD. For example, to what extent is social anxiety in ASD a ‘normal’ reaction to peer isolation / bullying as a result of impairment in social interaction? Under this scheme the direction of causality might be as follows: poor social functioning causes anxiety which causes hyper-activity in the amygdala. Turning this on its head, to what extent is anxiety or social anxiety caused by hyper-arousal which has neuropathology as its origin? Under this scheme, pathology in the amygdala causes amygdala hyper-activity and autonomic hyper-arousal which leads to anxiety. It may also be the case that elements of both schemes are operating, and interacting, within the same individual. For example, amygdala pathology may pre-dispose an individual to hyper-responsiveness to anxiety-inducing stimuli. As well as causing some social problems by itself, this initial hyper-activity may be reinforced by social isolation resulting from autistic symptoms of independent origin. The now heightened arousal / anxiety levels could then lead to further problems with social interaction, which causes more social isolation and therefore greater arousal / anxiety, and so on in a positive feedback loop.
Although the preceding discussion is highly speculative, it highlights gaps in the hyper-active model which need to be answered if the model is to provide a satisfying description of the relationship between amygdala hyper-activity, anxiety and social cognitive impairment in ASD.

**Pre-disposition to amygdala hyper-activity and anxiety in ASD**

If there is a pre-disposition to amygdala hyper-activity and/or anxiety in ASD, it would be interesting to explore its origin. One intriguing possibility is that it is related to the serotonin transporter (5-HTT) polymorphism. The short (s) allele of the 5-HTT gene has reduced transcriptional efficiency compared to the long (l) allele (Murphy et al., 2004). In members of the general population, the s allele has been associated with increased anxiety-related personality traits (Schinka et al., 2004; Sen et al., 2004), increased autonomic response to stress (Williams et al., 2001b), increased amygdala reactivity to emotionally salient stimuli (Bertolino et al., 2005; Hariri et al., 2005) and smaller amygdala volumes (Pezawas et al., 2005). In children, possession of two copies of the s allele is associated with increased shyness, a precursor to social anxiety (Battaglia et al., 2005), and in socially anxious adults, the s allele is associated with increased symptom severity and heightened amygdala excitability (Furmark et al., 2004). In addition, there is some evidence that the s allele is over-transmitted in ASD (Devlin et al., 2005). Together, these results suggest that possession of an s allele may pre-dispose individuals with an ASD to several aspects of the hyper-active model: namely, social anxiety, heightened autonomic and amygdala activity and decreased amygdala volume. Genotyping of my AS subjects for the 5-HTT polymorphism is currently underway, but unfortunately was not completed in time for inclusion in this thesis.
An alternative hyper-active amygdala model?

The current hyper-active amygdala model, expounded by Davidson and colleagues (Dalton et al., 2005; Nacewicz et al. in press), assumes that amygdala hyper-activity and autonomic over-arousal comes in response to (social) stimuli. Therefore, by avoiding the stimuli in question, an individual can prevent experiencing aversive over-arousal. However, there may be an alternative scheme where the amygdala and autonomic system are constantly hyper-active. If this were the case then it would be difficult to discern a signal indicating the presence of a significant stimulus over the background noise: salience signals from the amygdala would be essentially meaningless and may come to be ignored by the rest of the brain. In effect, the amygdala would fail to flag the relevant stimuli as significant and to modulate processing in other brain regions accordingly. This is exactly the same pathway to social cognitive impairment proposed by the hypo-active amygdala model (Schultz et al., 2000b; Schultz, 2005), albeit by a different aetiology. In other words, this ‘alternative hyper-active mode’ may be able to merge aspects of both the hypo- and hyper-active models into a single entity.

Support for this alternative theory in the literature is limited, but Hirstein et al. (2001) propose a similar model to explain what they termed “type A” autistic children. These children showed generally higher autonomic responses to a wide-range of stimuli compared to normal controls, but their SCR responses, although large, did not discriminate between a face and a paper cup. As discussed earlier, Hirstein et al.'s (2001) work has a number of methodological problems and has not been repeated, but it does highlight the possibility of an alternative hyper-active model.
This alternative hyper-active model could potentially explain a number of the findings in this thesis – for example the attentional blink results presented in chapter 6 and the higher rates of anxiety in ASD presented in chapter 5. It may also explain the correlation between higher social anxiety and reduced eye fixation and fear score – individuals with the highest hyper-activity would have the highest anxiety and also the most acute failure to signal social stimuli as significant. Amygdala atrophy to allostatic load could also apply equally to both hyper-active models. What the alternative model is unable to explain is the finding of a higher autonomic response to eyes versus mouths in my AS sample and the correlation between the size of this difference and low eye fixation, poor fear recognition and smaller amygdala volume. It will be remembered though that I found this correlation with one type of autonomic measurement but not the other. Therefore, differentiating between the two alternative hyper-active models is yet another reason why it is imperative to conduct an experiment measuring the amygdala activity and autonomic responses of a large sample of ASD individuals to a wide variety of social and non-social stimuli in a well controlled manner.

**Lack of association with autistic symptoms**

In AS, neither fear recognition ability, the percentage of fixations made to the eyes, anxiety level or magnitude of amygdala atrophy correlated with the severity of autistic symptoms, as measured by either the AQ or the ADOS. This obviously presents a problem for the model communicated in the preceding pages: if a failure to attend to social stimuli, poor fear recognition etc are supposed to be indicative of social cognitive impairment then one would expect this to be reflected in ADOS or AQ scores or, at least, in those sub-scales of these instruments which measure problems with reciprocal social interaction and communication.
A potential explanation may lie with the instruments themselves. The AQ is a self-report measure and some subjects may lack full insight into their condition (indeed, it may be the worst affected cases that most lack insight). The output from the ADOS is somewhat categorical and it could be argued that it is not able to discriminate between subtle differences in social impairment. Arguing against this though is the fact that there was a large spread in ADOS scores from mildly to severely affected. Still, a measure such as the ADI-R or 3-DI may have yielded more promising results: Nacewicz et al. (in press) found that both failure to fixate eyes and amygdala atrophy were associated with higher scores on the ADI-R. However, their sample consisted of low functioning autistic subjects. Perhaps for high functioning AS subjects more sophisticated tools are required that, rather than looking for autistic symptoms per se, measure subtle impairments in social interaction. An appropriate tool might monitor behaviour in a (staged) naturalistic, complex social interaction, for example. If such tools exist I am not aware of them but it seems that they would be a useful addition for social cognitive research.

However, it is perhaps more likely that there is nothing at fault with the sensitivity of the ADOS or AQ. Rather, inattention to socially relevant stimuli, and the social-perceptual deficits that ensue, may simply not be sufficient to cause problems in day to day interaction and communication. There may exist a multitude of compensatory strategies that allow for appropriate interaction in spite of problems with social perception. In addition, as well as social cognitive deficits, individuals with an ASD are known to have difficulties with executive function (Pennington and Ozonoff, 1996) and with integrating details into meaningful wholes ('weak central coherence', Happe and Frith, 1996). These deficits may reduce the ability to compensate for social perceptual problems. In this

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20 The ADOS has an element of staged social interaction but it is of a rather simple nature.
framework, social-perceptual, executive and central coherence deficits interact such that ‘multiple insults’ are required to produce the profound difficulties in social interaction often seen in ASD. To predict the severity of autistic symptoms in ASD, measures of all three factors may be required. In other populations where social perception problems exist (LFS individuals for example) the lack of any accompanying impairment in executive or central coherence functions may allow the full scope of compensatory strategies to operate, preventing the emergence of measurable autistic-like deficits in social interaction and communication.

However, LFS did show deficits on a theory of mind task, indicating that their impairments do not stop at basic social-perception but dig deeper into social cognition, even if they do not permeate strongly into day to day interaction. Clearly, the true scope of social cognitive impairment in LFS both in terms of laboratory based tests and everyday functioning needs to be examined in greater depth. Similarly, with ASD the mapping of laboratory demonstratable social-perceptual / social-cognitive impairment onto real world social ability, perhaps via interaction with other core autistic deficits such as executive function, should be a priority. Information of this kind could have important consequences for treatment of social difficulties in this population.

**Future directions**

Throughout this and earlier chapters I have suggested a number of experiments which would usefully carry the project forward. I will recap on the most important here before making some new suggestions for potentially useful experiments.

1) The most vital experiment would be one that makes a proper assessment of amygdala and autonomic reactivity in ASD in response to a variety of social and non-social
stimuli. There have obviously been experiments measuring, for example, amygdala activity to faces in ASD, but none of these have carefully controlled and manipulated the direction of the subjects’ attention: as I have shown in this thesis and others have commented before me (e.g. Dalton et al., 2005), this is absolutely essential, because ASD subjects may be avoiding or missing the most emotionally salient parts of the stimulus (Dalton et al., 2005; Klin et al., 2002; Pelphrey et al., 2002). This experiment would help discriminate between the two models of amygdala involvement in ASD, which have been discussed at length in this thesis (the hyper- and the hypo-active models), and would help investigate the possibility of an alternative hyper-active model, which I suggested earlier in this chapter. Large samples should be used because of the possibility that more than one of the models is in operation, but in different populations of ASD (Hirstein et al., 2001). As well as an age- and gender-matched control group, ASD subjects should also be compared to groups of anxious and socially anxious individuals. This would allow an investigation of the extent to which abnormalities in amygdala and/or autonomic reactivity in ASD are primary to the condition, rather than secondary, as a result of co-morbid anxiety. To be done properly, this experiment would be demanding, especially in terms of making sure that all subjects attend to the stimuli in the same way, but, in my opinion, it could prove extremely beneficial in terms of understanding the role of the amygdala in ASD.

2) It would be useful to conduct a similar experiment with LFS and NFS males from the general population, especially measuring amygdala activity to faces while manipulating where on the stimulus the subjects are fixating (i.e. the eyes or the mouth). This would help in discerning the causes for reduced eye fixation in LFS: could it be along the same lines as those suggested for ASD, i.e. is eye fixation associated with hyper- or hypo-active activation of the amygdala compared to
controls? Or, is there no difference in amygdala reactivity between LFS and NFS, suggesting that reduced eye fixation is caused by a factor not related to emotional salience or the amygdala? This experiment would also help clarify the fMRI results presented in chapter 3: do LFS and NFS brains react differently to the same visual input or do LFS individuals fixate the stimuli differently, therefore receiving different visual input than NFS?

3) To gain a broader picture of emotion recognition in general and fear recognition in particular amongst LFS and AS subjects, it would be interesting to compare the cognitive strategies used by these individuals to normal controls when completing the Ekman-Friesen test of facial affect. This would be especially illuminating for those AS subjects who spend very little time fixating the eyes yet still correctly identify a high proportion of fearful faces (see chapter 4, page 160). The Bubbles task would be a good method for doing this, as it would provide a summary of the information used by each individual to identify the different emotions (Smith et al., 2005). Specific hypotheses about a varying reliance on the eyes for different subject groups could be investigated by digitally removing these features from the faces and measuring the change in fear recognition. For example, one might predict that those AS subjects with a high fear score despite low eye fixation would show no detriment in fear recognition but that other AS subjects, who normally fixate the eyes a lot, would show lower scores with the eyes removed. These methods should generate some hypotheses regarding the different kinds of cognitive strategies being employed in the Ekman-Friesen task. These could then be confirmed by a new analysis of the eyetracking data already taken as part of the experiments presented in chapters 3 and 4.
4) The hyper- and hypo-active amygdala models of ASD provide neurodevelopmental accounts of the disorder. Therefore, the degree to which they can be investigated by cross-sectional study is limited. Longitudinal studies will be required, looking, for example, at the volume of the amygdala as age progresses.

5) As discussed in the last section and in chapter 5, the fact that high social anxiety in members of the general population has been associated with hyper-vigilance of social stimuli and high fear recognition offers a challenge to the hyper-active model. I suggested that the apparent discrepancy might be explained by different coping styles in AS or by an inverted ‘U’ relationship between vigilance and social anxiety (e.g. see chapter 5, page 184). Investigating these possibilities will be an important step towards refining the hyper-active model.

6) Again, as discussed in the last section, fear recognition and associated variables such as failure to fixate the eyes did not predict the level of an individual’s impairment in reciprocal social interaction and communication, as measured by the ADOS and AQ. It will be important for the theoretical understanding of ASDs to investigate how social-perceptual and social-cognitive deficits map on to day to day difficulties with social cognitive impairment. This may require novel methods for assessing real world social functioning that perhaps attempt to mimic the complexity of a genuine social situation.

The suggestions above are a selection of some of the possible future directions that I have already discussed earlier in this thesis. In the following section I will discuss some ideas for future experiments which I have not considered previously.
I have shown that reduced fixation of the eye region is associated with poor fear recognition in AS and LFS. It would also be interesting to see if the amount of time spent fixating eyes correlates with ability on other tasks thought to require the processing of information from this region of the face – Baron-Cohen’s ‘reading the mind from the eyes’ task (Baron-Cohen et al., 2001a) would be one such example. Another example might be the ability to differentiate between Duchenne (true enjoyment) and non-Duchenne (faked/social) smiles. Duchenne smiles are distinguished by contraction of the *orbicularis oculi* muscles, which produces characteristic ‘crow’s feet’ wrinkling around the eyes (Duchenne de Boulogne, 1862/1990;Ekman et al., 1990). Normal subjects are known to spend a prolonged time fixating the wrinkling around the eyes when viewing smiling compared to neutral facial expressions (Williams et al., 2001a). Both LFS and low-eye-fixating AS subjects correctly identify almost 100% of happy expressions (see chapters 3 and 4) but it would be interesting to see if they have more difficulty distinguishing Duchenne from non-Duchenne smiles and if this could be associated with a failure to fixate the eye area.

**Limitations**

There are a number of limitations to the methodology used in this thesis which are worthy of further consideration. Often, these reflect limitations which are common in the fields of social cognitive neuroscience and AS research. One area of difficulty concerns the recruitment of AS subjects. It is often difficult to find suitable adult participants and many research groups rely on adverts in AS related publications or on volunteers from AS social groups, as I have done. There is instant selection bias here in that one is only accessing those individuals who choose to read the relevant publications or decide to attend the social groups. However, a more important source of selection bias might be
that those who choose to take part in studies may have different characteristics than those who do not – one might hypothesise that those who do take part may be more socially able, for example. I do not have any formal data on this, but in the course of subject recruitment I visited a number of AS social groups to meet potential participants. Typically, only ~20% of those present volunteered to take part in my studies and it seemed to me that these were often some of the least socially impaired individuals. Added to this is the fact that my experiments required travelling to a busy area of central London. I can recall a number of subjects who were happy to be visited in their homes but were put off by the thought of this journey – again, it seemed that it was the least impaired who were willing to make the journey. Of course, much of the above is anecdotal and some formal measurement of these potential biases is required, but it would be difficult to assert that my AS group represented a random sample of the population, making it difficult to infer strong conclusions about the condition as a whole.

Another potential source of bias is the heterogeneity within AS and the broader ASD phenotype, both in terms of the severity of impairment in differing areas of the ‘triad’ (Wing and Gould, 1979) and, potentially, in the aetiology and pathology relating to these impairments. The problem is compounded by the typically small sample sizes used in studies of ASD and by the different ways in which diagnosis can be confirmed. It seems likely that one sample of AS subjects may be very different from another. It is difficult to see how this problem can be resolved before a deeper understanding of the nature of the heterogeneity has been reached, which is perhaps why several groups are making it a focus of their research (e.g. Hrdlicka et al., 2005; Klin et al., 2005; Verte et al., 2006b; Verte et al., 2006a).
Finally, due to the nature of the topic under study, the research presented here has been correlational rather than experimental. Along with case studies, correlational research is common (and often unavoidable) when the aim is to study a particular disorder. With this kind of data it is, of course, not possible to conclusively prove causality and it should therefore be remembered that conclusions should be somewhat tentative and reference to theory and converging evidence is of particular importance.

**Concluding remarks**

As with many research studies, this project has raised far more questions than it is able to answer, and limitations in design, time and the availability of research participants have restricted the scope of its conclusions. Nevertheless, the project has shown the potential benefit of using theoretical accounts to inform research into the involvement of the amygdala in social cognition and has been able to suggest several avenues for exploring this further. It is hoped that these will prove fruitful areas of research in the near future.
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