INTRODUCTION
1.1 General Introduction

In 1939 Kluver and Bucy demonstrated that the bilateral removal of the medial temporal lobes, including the amygdala and hippocampus, had a dramatic effect on the behaviour of rhesus monkeys (Kluver and Bucy, 1939). Operated animals exhibited a number of changes in behaviour including excessive tameness, indiscriminate phagic and sexual behaviour and a failure to recognise familiar objects. Weiskrantz subsequently investigated the consequences of more selective lesions to the amygdala and found that amygdalectomised animals exhibited specific components of the syndrome observed by Kluver and Bucy, in particular tameness and an apparent lack of fear (Weiskrantz, 1956). Further experimental studies of the same subjects showed that they were impaired in their learning of an association between a previously neutral auditory stimulus and an unpleasant electric shock (Weiskrantz, 1956). In parallel with these studies Rosvold and others demonstrated a role for the monkey amygdala in social interactions with lesioned animals exhibiting decreased aggression and losing their status in the dominance hierarchy in social groups (Mirsky, 1969; Plotnik, 1968; Rosvold et al., 1954).

Over the following decades a large number of experiments have confirmed a central role for the amygdala in aspects of emotional and social processing. Most progress has been made in the study of aversive fear conditioning in rats and other mammals (LeDoux, 2003; LeDoux, 2000; Phelps and LeDoux, 2005; Rodrigues et al., 2004). In these tasks an association is learnt between a previously neutral stimulus (such as a tone) and an aversive stimulus (for example a shock to the feet) such that after paired presentation of these stimuli the neutral stimulus itself comes to elicit
responses associated with the aversive stimulus alone. Research has demonstrated an essential role for the amygdala in encoding such associations (LeDoux, 2000). In particular the basolateral nuclei of the amygdala have been shown to have a primary role in the encoding of aversive associations, and long-lasting changes in synaptic function in this region have been shown to accompany aversive conditioning in this region (Rogan et al., 1997). Recent studies have begun to determine the molecular changes that accompany such alterations in synaptic function in the basolateral amygdala (Rodrigues et al., 2004). Other amygdala nuclei including the central nucleus are required to orchestrate autonomic responses to emotional stimuli in response to inputs from the basolateral region (LeDoux, 2000).

For many years little progress was made in understanding the role of the human amygdala in behaviour and cognition. The study of human amygdala function was impeded by both the rarity of identified subjects with selective damage to this brain region and the corresponding absence of specific validated neuropsychological tests of amygdala function. However the identification of subjects with selective amygdala damage resulting from the rare Urbach-Weithe disease, along with a small number of subjects with relatively selective surgical lesions, has allowed the function of the human amygdala to be directly investigated (Adolphs et al., 1994). Subsequent studies demonstrated a selective requirement for the human amygdala in a number of domains of emotional and social functioning, including the processing of emotional and social information from faces and the encoding of emotional memories (Adolphs et al., 1998; Adolphs et al., 1994; Cahill et al., 1995; LaBar and Cabeza, 2006). The involvement of the amygdala in these behaviours has subsequently been confirmed using functional brain imaging techniques (Hamann et al., 1999; Morris et al., 1996; Winston et al., 2002).
More recently attention has turned to studying the role of the amygdala in human illnesses. Amygdala pathology has been implicated in a number of disorders including depression, bipolar affective disorder and autism (Altshuler et al., 2005; Baron-Cohen et al., 1999; Drevets, 2000). However increasing evidence suggests that amygdala function may be abnormal in psychotic illnesses, in particular schizophrenia (Lawrie et al., 2003; van Rijn et al., 2005). Meta-analyses of brain imaging studies have shown abnormalities of amygdala structure in schizophrenia (Lawrie and Abukmeil, 1998; Wright et al., 2000), whilst individuals with temporal lobe epilepsy originating in the amygdala describe psychotic symptoms that parallel those seen in acute schizophrenia (Slater and Beard, 1963; Trimble and Van Elst, 2003). Furthermore the affective and social deficits seen in monkeys following amygdala lesions show similarities with the negative symptoms of schizophrenia. The purpose of the experiments described in this thesis was to investigate amygdala function in individuals with schizophrenia by studying their performance on tests of emotional and social function known to require the integrity of the amygdala.

In order to introduce these experiments four areas are reviewed in this chapter. Firstly the anatomy of the amygdala, with particular reference to its afferent and efferent connections is considered. Secondly neuropsychological tests of amygdala function in humans are outlined. Thirdly structural studies of the amygdala in patients with schizophrenia and their relatives are reviewed. Finally, existing evidence regarding the performance of subjects with schizophrenia on tests of amygdala function is discussed.
1.2 Amygdala anatomy

The amygdala is an almond-shaped structure lying in the anteromedial part of the temporal lobe that was first described in the early 19th century by Burdach. It lies ventro-medial to the striatum and anterior to the ventral portion of the hippocampal formation. The amygdala comprises a complex of 13 nuclei which can be broadly divided into three principal groups based on cellular morphology and connectivity – the basolateral group, the centromedial group and the superficial cortical-like group (Amaral et al., 1992; Sah et al., 2003). The basolateral group (including the lateral, basal and accessory basal nuclei) comprises cells which, whilst lacking a laminar organisation, are homologous to cortical pyramidal and non-pyramidal neurons (Sah et al., 2003). Pyramidal-like neurons in this region use glutamate as a primary neurotransmitter (Smith and Pare, 1994). In contrast the neurons of the centromedial group (comprising the central and medial nuclei) resemble the medium spiny neurons of the striatum and are predominantly GABAergic (McDonald and Augustine, 1993). The superficial cortical-like nuclei (incorporating the cortical nucleus, the periamygdaloid complex and the nucleus of the lateral olfactory tract) have a laminar organisation that resembles the adjacent olfactory cortex (Sah et al., 2003).

The organisation of intra-amygdaloid connections is complex and has been mainly established from studies in the rodent (Pitkanen et al., 1997; Sah et al., 2003). Fewer studies have been conducted in primates, but the available evidence suggests that a similar pattern of intra-amygdala connectivity is also found in higher mammals (Amaral et al., 1992). Whilst a full review of these connections is beyond the scope of the present thesis, an overall picture emerges of lateral to medial information flow within the amygdala which is consistent with potential functional specialisations of
different amygdaloid nuclei (Pitkanen et al., 1997; Sah et al., 2003). There are extensive reciprocal connections within the nuclei of the basolateral complex, all of which project to the central nucleus. The central nucleus itself however sends only meagre reciprocal connections to the basolateral region, with its main projections being to regions of the autonomic nervous system outwith the amygdala. These patterns of connections support a model in which the basolateral complex is the primary site of associative learning in the amygdala, which can influence autonomic function via connections to the central nucleus (Phelps and LeDoux, 2005). The intra-amygdala connections of the superficial cortical-like nuclei have been much less extensively investigated although the available evidence suggest that these regions also receive information from the basolateral complex (Pitkanen et al., 1997).

The afferent and efferent connections of the amygdaloid nuclei give an indication as to how they may contribute to emotional and social processing. The amygdala receives extensive afferents conveying sensory information from all modalities. This information is conveyed through both cortical and subcortical (largely thalamic) routes and is predominantly targeted to the basolateral and to a lesser extent central nuclei of the amygdala (Amaral et al., 1992; Sah et al., 2003). The main exception to this pattern is seen in the olfactory cortex which projects to the superficial cortical-like nuclei. The amygdala also receives important afferent connections from higher order (polymodal) cortical regions including the prefrontal cortex and medial temporal lobes. These connections are primarily targeted to the basolateral regions of the amygdala. The main afferents to the centromedial nuclei are from the hypothalamus and brainstem nuclei in the midbrain pons and medulla as well as from the basolateral nuclei. This central nucleus however has only sparse afferent
connections from sensory and polymodal cortices (Amaral et al., 1992; Sah et al., 2003).

The primate amygdala has a wide range of efferent connections (Amaral et al., 1992). The basolateral complex projects broadly to many cortical regions and has especially prominent projections to the prefrontal cortex and to medial temporal lobe memory systems including the hippocampus and perirhinal cortex. The basolateral nuclei also project to areas of association cortex such as the superior temporal gyrus and to limbic regions of the striatum including the nucleus accumbens (Amaral et al., 1992; Sah et al., 2003). In contrast the centromedial amygdala projects primarily to the hypothalamus and bed nucleus of the stria terminalis and to brainstem nuclei involved in the regulation of autonomic function such as the periaqueductal gray, parabrachial nucleus and nucleus of the solitary tract (Dong et al., 2001; Veening et al., 1984). In addition there are projections form the central nucleus to nuclei involved in ascending monoaminergic and cholinergic function including the substantia nigra, ventral tegmental area and nucleus basalis. The superficial cortical have extensive projections to olfactory cortical regions, reflecting their presumed role in olfactory processing (Sah et al., 2003).

The above description of the anatomy and connections of the amygdala gives an indication of how it may function in social and emotional processing. The amygdala receives extensive cortical and sub-cortical information regarding potentially emotionally relevant stimuli and has extensive efferent connections to prefrontal cortex and medial temporal lobe memory systems involved in cognition and memory. In addition the amygdala is able to modulate autonomic responses to emotional stimuli through the projections of the central nucleus to nuclei of the autonomic nervous system.
1.3 Neuropsychological tests of amygdala function

The identification of subjects with selective damage to the amygdala has led over the past 12 years to the development of specific neuropsychological tests of human amygdala function. These studies have shown that the human amygdala participates in social and emotional processing, paralleling its role in other primates. Tasks in which a role for the amygdala has been demonstrated by both lesion studies and functional neuroimaging studies represent particularly robust measures of amygdala function. Here I review evidence for the involvement of the amygdala in four tasks that meet this criterion of convergent evidence from both lesion and neuroimaging studies.

1.3.1 Facial emotion recognition

The publication in 1994 of a report detailing specific impairments in facial emotion recognition in a subject with selective bilateral amygdala damage due to Urbach-Weithe disease represented the first demonstration of a specific function of the human amygdala (Adolphs et al., 1994). The subject participated in a test in which the six primary facial emotions (happiness, sadness, anger, disgust, surprise and fear) had to be identified from pictures of faces. The status of these facial expressions as primary emotions expressed across a wide range of cultures had been previously demonstrated (Darwin, 1872; Ekman et al., 1969). Remarkably, the amygdala damaged subject showed a selective deficit in her ability to recognise the emotion of fear compared to matched brain-damaged control subjects. Importantly this deficit could not be explained in terms of a more general deficit in processing facial information, as the same subject showed a preservation of her ability to recognise the identity of faces.
(Adolphs et al., 1994). This deficit in recognition of the emotion of fear from faces in subjects with amygdala damage has been borne out in a subsequent analysis of nine subjects with amygdala damage tested on the same tasks (Adolphs et al., 1999). This larger study demonstrated not only robust deficits in the recognition of fear from faces but also more subtle impairments in the recognition of other facial emotions (Adolphs et al., 1999). The extent to which deficits in emotion recognition in subjects with amygdala damage are restricted to emotion expressed in faces has not been fully clarified, however some studies have shown similar deficits in recognising the emotion of fear from voices and gestures in subjects with amygdala lesions (Scott et al., 1997; Sprengelmeyer et al., 1999).

The involvement of the amygdala in the recognition of fear in facial expressions has been confirmed in functional neuroimaging studies. Morris and colleagues using positron emission tomography (PET) and Breiter and co-workers using function magnetic resonance imaging (fMRI) both demonstrated amygdala activation in response to faces expressing the emotion of fear compared to faces with a neutral emotional expression (Breiter et al., 1996; Morris et al., 1996). The finding of amygdala activation to fearful faces has subsequently been extensively replicated (Adolphs, 2003). Activation of the amygdala to the presentation of other facial emotions has been less conclusively demonstrated although some studies have identified amygdala activation in response to the presentation of faces expressing sadness (Blair et al., 1999) and anger (Whalen et al., 2001). In addition amygdala activation has been demonstrated to happy faces as a function of the personality traits of the observer (Canli et al., 2002). More recently, studies have suggested that the amygdala is activated in response to multiple emotional expressions (Fitzgerald et al., 2006; Winston et al., 2003).
The impairments in facial emotion processing seen in amygdala damaged individuals may at least in part relate to a failure to attend to cues from the eyes. Morris and co-workers demonstrated that amygdala activation could be elicited by presentation of the eyes alone from fearful faces, characterised by the presence of supra-pupillary exposure of the sclera (the “whites of the eyes”) (Morris et al., 2002). Adolphs and colleagues have extended this observation by using eye-tracking to demonstrate that subjects with amygdala damage fail to selectively attend to the eyes in fearful faces (Adolphs et al., 2005). Damage to the amygdala may therefore specifically impair the ability of subjects to attend to stimuli of particular social and emotional relevance.

1.3.2 Social cognition

The above studies have been extended to investigate the role of the amygdala in making social judgements beyond the recognition of basic facial emotions (Adolphs et al., 1998). In particular the involvement of the amygdala in making more complex social judgements from faces, such as whether an individual appears trustworthy or not, has been studied using both lesion and functional neuroimaging approaches (Adolphs et al., 1998; Winston et al., 2002). These more complex social stimuli cannot be simply reduced to the six primary facial emotions described above and represent a combination of emotional and non-emotional features.

Adolphs and co-workers demonstrated that subjects with amygdala damage are impaired in their ability to judge approachability and trustworthiness from faces in comparison to control subjects (Adolphs et al., 1998). Amygdala damaged subjects tended to rate faces as more approachable and trustworthy than control individuals. A
more general impairment in making social judgements in individuals with amygda
damage was suggested by a subsequent study which found that subjects with
amygdala damage were impaired on the identification of a range of social emotions
(such as guilt, admiration and flirtatiousness) from the eye regions of faces (Adolphs
et al., 2002). Notably in the latter study impairments in social judgement were found
to be greater than that for the six basic facial emotions.

The involvement of the amygdala in social cognition has been confirmed
using functional neuroimaging techniques. Winston and colleagues demonstrated that
amygdala activation is correlated with how untrustworthy a face is rated, even when
subjects were not asked to explicitly rate the faces on this dimension during scanning
(Winston et al., 2002). This result was interpreted as showing that the amygdala is
automatically engaged in response to threatening social stimuli even in the absence of
explicit judgement. Baron-Cohen and co-workers have also demonstrated amygdala
activation during explicit social judgements made from the eye region of faces
(Baron-Cohen et al., 1999). A particular role for the amygdala in learning the social
value of faces has been further demonstrated by imaging studies showing amygdala
activation to pictures of individuals who have previously acted in an untrustworthy
manner in a prisoner dilemma game (Singer et al., 2004).

Extensive evidence also supports the involvement of other brain regions, in
particular the superior temporal gyrus and prefrontal cortex in aspects of social
decision making (Adolphs, 2001; Allison et al., 2000; Amodio and Frith, 2006a;
Haxby et al., 2002; Winston et al., 2002). These regions, in collaboration with the
amygdala are considered to form part of a network of brain regions required for social
cognition (Brothers, 1990). Current theories suggest that different regions within this
network are specialised for different aspects of the processing of social information.
from faces (Adolphs, 2001; Bruce and Young, 1986; Haxby et al., 2000). The studies reviewed above demonstrate that the amygdala plays a central role in this network which includes, but may not be restricted to, an involvement in representing and identifying the emotional significance of social stimuli.

1.3.3 Emotional enhancement of episodic memory

Emotionally arousing events are better remembered than neutral events (Bradley et al., 1992). This ability to enhance episodic memory for events of emotional significance is clearly of adaptive value and has been shown to depend on the amygdala and its interaction with medial temporal lobe memory systems (McGaugh, 2004; Phelps, 2004). Individuals with amygdala damage have normal memory for non-emotional stimuli, but lack the enhancement of memory normally seen for emotional stimuli (Adolphs et al., 1997; Cahill et al., 1995). Animal studies have shown that the amygdala exerts its effect on emotional memory formation in part by mediating the memory-enhancing effects of both adrenergic and steroid stress hormones (McGaugh, 2000; McGaugh and Roozendaal, 2002; Roozendaal and McGaugh, 1996; Roozendaal et al., 1996). The amygdala is required for these hormones to exert their influence on medial temporal lobe memory systems including the hippocampus (McGaugh, 2004). Evidence suggests that stress hormones activate adrenergic receptors in the basolateral amygdala, which modulates the effect of these hormones on hippocampal consolidation (McGaugh and Roozendaal, 2002). A similar mechanism is likely to operate in human subjects where β-adrenergic receptor activation has also been shown to be necessary for the emotional enhancement of episodic memory (Cahill et al., 1994).
Neuroimaging studies support the hypothesis that the amygdala exerts its effect on emotional memory formation by modulating memory formation in medial temporal lobe memory systems including the hippocampus. Thus increased amygdala activation during the viewing of emotional scenes is correlated with both enhanced hippocampal activation and better subsequent memory (Canli et al., 2000; Dolcos et al., 2004; Hamann et al., 1999). Notably the correlation of amygdala activation with enhanced memory is dependent on the intensity of emotional arousal produced by the stimulus, rather than its emotional valence (positive or negative), suggesting a general role for the amygdala in mediating memory enhancement for all emotionally arousing stimuli (Canli et al., 2000; Hamann et al., 1999; Kensinger and Corkin, 2004).

In summary a specific role for the amygdala in enhancing episodic memory for emotional arousing events has been shown in both lesion and neuroimaging studies. This modulatory effect is mediated through enhancement of memory formation in other medial temporal lobe memory systems, in particular the hippocampus. Such interactions are likely supported by the extensive connections between the amygdala and hippocampus reviewed above.

1.3.4 Pavlovian fear conditioning

Pavlovian, or classical, conditioning is the process through which a previously neutral stimulus (the conditioned stimulus or CS), by virtue of paired presentation with a biologically significant event (the unconditioned stimulus or US) comes itself to elicit a characteristic response (the conditioned response or CR). The CR often resembles the response produced by the presentation of the US alone, known as the unconditioned response (UR).
The role of the amygdala in Pavlovian conditioning has been extensively studied in animals (Phelps and LeDoux, 2005). These studies have primarily used Pavlovian fear conditioning techniques in which the CS is a simple stimulus such as a tone and the US is typically an aversive mild electric shock to the feet. Conditioning is measured using simple autonomic and behavioural measures such as heart rate, startle and freezing. Overall a large literature has demonstrated an essential requirement for the amygdala in Pavlovian fear conditioning, and a particular role for the basolateral complex of the amygdala in forming new CS-US associations (LeDoux, 2003). In contrast the central nucleus of the amygdala primarily acts as an orchestrator of autonomic responses to the CS, although under certain circumstance it too may mediate associative learning (Gallagher et al., 1990; Hall et al., 2001; Parkinson et al., 2000).

Human subjects with amygdala damage also show impairments in Pavlovian fear conditioning (LaBar and Cabeza, 2006; LaBar et al., 1995). For example, subjects with unilateral amygdala damage show a lack of conditioned skin conductance responses to a tone previously paired with a mild aversive electric stimulation to the skin (LaBar et al., 1995). The deficit in conditioning seen following amygdala damage does not simply represent an impairment in episodic memory for the conditioning, as Bechara and colleagues demonstrated a double-dissociation between impairments in episodic memory for the conditioning stimuli resulting from hippocampal damage and deficits in fear conditioning itself resulting from amygdala damage (Bechara et al., 1995).

The involvement of the human amygdala in Pavlovian fear conditioning has been further confirmed by neuroimaging studies. Two studies both using event-related fMRI techniques have demonstrated specific activation of the amygdala to the
presentation of an aversively conditioned CS (Buchel et al., 1998; LaBar et al., 1998). These studies also identified a neural network activated during the acquisition of Pavlovian fear conditioning which included the periamygdaloid cortex, thalamus, sensory neocortex and anterior cingulate gyrus/medial prefrontal cortex as well as the amygdala itself.

Results from both lesion and neuroimaging studies therefore support the involvement of the amygdala in the formation of conditioned associations in Pavlovian fear conditioning procedures. These findings suggest that the amygdala may operate more generally in social and emotional processing to encode the reinforcing or motivational value of stimuli (Weiskrantz, 1956).

1.3.5 Summary

The evidence reviewed above demonstrated a requirement for the human amygdala in four separable tasks: facial emotion recognition; social cognition; emotional enhancement of episodic memories and Pavlovian conditioning. Each of these tasks meets the criterion of sensitivity to amygdala damage and demonstration of activation of the amygdala in functional neuroimaging studies. These tasks therefore represent a set of neuropsychological tests which can be applied to investigate amygdala function in neuropsychiatric disorders.

Before reviewing existing data on the performance on patients with schizophrenia on these tasks I will first examine the literature regarding the structure of the amygdala in individuals with schizophrenia.
1.4 Amygdala structure in schizophrenia

The advent of magnetic resonance imaging (MRI) in the late 1970s opened the door to the investigation of subtle abnormalities in structure of grey and white matter in patients with psychiatric disorders including schizophrenia. Since the development of MRI a number of studies have investigated regional brain volumes, including amygdala volume, in schizophrenia (Lawrie and Abukmeil, 1998; Wright et al., 2000). The majority of studies have relied upon ascertaining brain volumes using a pre-defined region of interest approach. This method however is both limited in terms of the number of regions that can be examined and the difficulty in reliably identifying landmarks associated with particular brain structures. The latter problem is particularly acute for the amygdala, which lacks clear-cut anatomical boundaries on MRI (Brierley et al., 2002). This has led some groups to report volumes for the amygdalo-hippocampal complex rather than for the amygdala alone. However the advent of statistical approaches for comparing brain structure on a voxel-by-voxel basis, such as voxel based morphometry (Ashburner and Friston, 2000), has allowed a systematic examination of differences in structure between patient and control groups without the need to manually identify anatomical landmarks and this approach has therefore permitted a more objective approach to be taken to the determination of amygdala structure in schizophrenia.

Since the introduction of MRI over 60 controlled studies of regional brain volumes in schizophrenia have been conducted and a number of meta-analyses of these studies have been published (Lawrie and Abukmeil, 1998; Nelson et al., 1998; Wright et al., 2000). Overall these meta analyses support a reduction in amygdala volume in patients with schizophrenia of the order of 6-10%. Whilst this is a
relatively small reduction in overall volume, it represents one of the largest and most consistently replicated changes in regional brain volume identified in patients with schizophrenia (Wright et al., 2000). Notably this reduction in amygdala volume has been confirmed using voxel-based morphometry in first episode subjects (Job et al., 2002) making it unlikely that these findings can be accounted for by either observation bias or the effects of prolonged illness and treatment.

Reductions in amygdala volume have also been demonstrated in studies of the unaffected and high risk relatives of subjects with schizophrenia. Thus a number of studies have demonstrated reductions in the volume of the amygdala (Keshavan et al., 1997; Seidman et al., 1999; Seidman et al., 1997) or the amygdalo-hippocampal complex (Keshavan et al., 2002; Lawrie et al., 1999; Lawrie et al., 2001; O'Driscoll et al., 2001; Schreiber et al., 1999) in the relatives of subjects with schizophrenia. These results suggest that abnormalities in amygdala structure may represent part of a heritable vulnerability state for schizophrenia. Longitudinal studies suggest that abnormalities in amygdala structure precede the onset of the disorder in vulnerable individuals and do not progress during the development of illness (Job et al., 2005; Lawrie et al., 2003; Pantelis et al., 2003).

The literature on amygdala structure in post-mortem tissue from patients with schizophrenia is much more sparse. An early study reported significant reductions in amygdala size in the post-mortem brains of subjects with schizophrenia using planimetry (Bogerts et al., 1985). However this finding has not been replicated in subsequent studies (Chance et al., 2002; Heckers et al., 1990; Pakkenberg, 1990). All these studies have however examined amygdala volume in small numbers of subjects, and may therefore have been underpowered to detect structural differences of the order identified in MRI studies. In addition the available post-mortem studies vary
considerably in both the techniques used to examine amygdala structure and the nature and quality of the post-mortem tissue studied. Even fewer studies have addressed the issue of whether there are differences in the cellular or chemical anatomy of the amygdala in individuals with schizophrenia, although reports have suggested a decrease in the receptors for thyrotropin-releasing hormone (Lexow et al., 1994) and asymmetric dopamine levels (Reynolds, 1983).

Overall these studies support the view that amygdala volume is decreased in schizophrenia and suggest that this abnormality may represent part of a heritable vulnerability state for the disorder. The issue of whether such structural changes have effects on amygdala function in schizophrenia will be discussed next.
1.5 Amygdala function in schizophrenia

In this section the existing literature on the performance of patients with schizophrenia on tasks dependent upon amygdala function is reviewed for the four tasks identified above. In addition, where available, data from functional neuroimaging studies regarding amygdala activation in subjects with schizophrenia performing these tasks is also discussed.

1.5.1 Facial emotion recognition

A large number of studies have been conducted examining the ability of subjects with schizophrenia to recognise facial emotions (Edwards et al., 2002; Mandal et al., 1998). These studies have in general demonstrated impairments in facial affect recognition in schizophrenia. However the available studies have varied greatly in the nature of stimuli used and the methodology employed (Edwards et al., 2002; Mandal et al., 1998). In addition these studies have differed in the nature of the clinical population recruited, particularly in factors such as chronicity of illness and symptom status. There has been a significant degree of heterogeneity in the results of these studies and a number of issues regarding the nature of the deficit in facial affect processing in schizophrenia therefore remain unresolved. These are considered in more detail below.

Firstly, it is unclear whether the deficit in facial emotion processing is equal across all emotional categories. A number of studies have suggested a general deficit in the recognition of all facial emotions (Cramer et al., 1989; Feinberg et al., 1986; Heimberg et al., 1992; Walker et al., 1984) whilst others have indicated a more specific impairment in the recognition of negative emotions akin to that seen following amygdala
damage (Borod et al., 1993; Evangeli and Broks, 2000; Mandal and Palchoudhury, 1985). This may in part relate to differences in task difficulty, as happiness is the most readily identified emotion, even in control subjects.

Secondly, a number of authors have called into question whether the impairments seen in facial affect recognition are specific to emotional stimuli or represent part of a more general impairment in face processing. Several studies have shown that patients with schizophrenia have deficits in facial recognition tasks suggesting that the observed deficits in facial emotion recognition may derive from a more global impairment in the processing of facial stimuli (Archer et al., 1994; Feinberg et al., 1986; Hooker and Park, 2002; Kerr and Neale, 1993; Martin et al., 2005; Onitsuka et al., 2003; Salem et al., 1996). However other studies have not shown such a generalized impairment (Heimberg et al., 1992; Schneider et al., 2006; Walker et al., 1984). The discrepancies between these studies may in part relate to differences in methodology, with greater deficits in general face processing observed in tasks with higher mnemonic or attentional demands (Feinberg et al., 1986; Onitsuka et al., 2003). However such factors cannot account for all such deficits as some studies have shown deficits in tasks with low mnemonic and attentional demands such as the Benton test of facial affect recognition (Mueser et al., 1996). Strong evidence for a specific deficit in facial affect processing over and above any more general impairment in face processing is however provided by studies which have shown that deficits in facial affect processing remain even after controlling for differences in performance in face-recognition tasks (Borod et al., 1993; Kucharska-Pietura et al., 2005). These results indicate that whilst patients may have some general deficits in the processing of face stimuli, these cannot fully account for the observed impairments in facial affect processing.
Finally, it remains to be clarified whether the deficits in facial emotion recognition seen in schizophrenia are stable over time (a trait effect) or are associated with specific clinical symptoms (a state effect). A number of studies have related impairments in facial affect recognition in schizophrenia to the presence of positive symptoms (Cutting, 1981; Gessler et al., 1989; Kohler et al., 2000; Weniger et al., 2004), although some studies have also found an association with negative symptoms (Kohler et al., 2000; Sachs et al., 2004). A further group of studies have demonstrated a persistent deficit across the course of the illness, independent of clinical state (Kucharska-Pietura et al., 2005; Wolwer et al., 1996). The relationship of facial emotion recognition to clinical state in schizophrenia therefore remains uncertain.

Functional neuroimaging studies of amygdala activation in subjects with schizophrenia using emotional faces as stimuli have also produced heterogeneous results. Some studies have demonstrated decreased amygdala activation to facial emotions in patients with schizophrenia (Gur et al., 2002; Johnston et al., 2005; Phillips et al., 1999; Williams et al., 2004), whilst others have shown increased amygdala activation (Holt et al., 2006; Holt et al., 2005; Kosaka et al., 2002). In addition some studies showing decreased amygdala activation have not shown any deficits in performance on emotion recognition tasks (Gur et al., 2002). In general the interpretation of the neuroimaging studies, like the neuropsychological studies outlined above, is made more difficult by the use of differing patient groups and task designs across studies.

Overall the above studies support a deficit in facial emotion recognition in schizophrenia. However the heterogeneity of the findings from both neuropsychological and neuroimaging studies limits the strength of any conclusions that can be drawn regarding amygdala function in schizophrenia from studies of facial emotion recognition alone.
1.5.2 Social cognition

Previous studies of social cognition in schizophrenia have shown deficits in tasks in which subjects with schizophrenia have been required to make judgements regarding the social information conveyed in videotaped or scripted interactions, role play or problem solving tasks (Penn et al., 1997). These deficits in social cognition could not be accounted for by more general measures of information processing or IQ, suggesting that social cognition may represent a separable cognitive domain in which patients with schizophrenia have specific deficits (Brothers, 1990; Ostrom, 1984; Penn et al., 1997). Impaired social judgement in schizophrenia has also been shown to be stable across the course of the illness (Penn et al., 1997) and to relate to more general measures of social behaviour (Corrigan and Toomey, 1995; Penn et al., 1996).

There have however thus far been no studies of the ability of patients with schizophrenia to make social judgements using tasks previously shown to depend on amygdala function, such as judgements of approachability and trustworthiness from faces (Adolphs et al., 1998). There have also been no neuroimaging studies of patients with schizophrenia using social judgement tasks. Given the lack of information regarding the neural substrates of the tasks described above it is therefore not currently possible to conclude whether the pattern of deficits in social cognition seen in patients with schizophrenia reflects that seen following amygdala damage.
A small number of previous studies have investigated the emotional modulation of memory for words in subjects with schizophrenia (Calev and Edelist, 1993; Danion et al., 2003; Koh et al., 1976; Mathews and Barch, 2004). Some of these studies have shown a relative preservation of emotional memory effects in schizophrenia in terms of both recall (Calev & Edelist 1993; Koh et al., 1976; Mathews and Barch 2004) and recognition (Mathews and Barch, 2004) whilst others have shown selective deficits in recognition memory (Danion et al., 2003). These studies may however not have been optimally designed for the investigation of amygdala function. In particular the use of word rather than pictorial stimuli in these previous studies may have limited the degree of emotional arousal elicited by the stimuli. In addition many of these studies have examined memory at short recall intervals (Danion et al., 2003; Koh et al., 1976; Mathews and Barch, 2004), although the effects of emotional arousal on memory consolidation are greatest after a delay (LaBar and Phelps, 1998).

There have been no previous studies of the performance of patients with schizophrenia on emotional memory tasks using affective scenes. Such scene stimuli have been used in the majority of neuroimaging studies of emotional memory and have been shown to produce reliable activation of the amygdala (Canli et al., 2000; Hamann et al., 1999). Well characterised emotional scene stimuli are available and have been shown to include pictures that are highly emotionally arousing (Lang et al., 1997; Lang et al., 1993). Studies using such affective scenes, with delayed memory tests, are required before robust conclusions can be drawn regarding the performance of patients with schizophrenia on tests of emotional memory.
There have been no functional neuroimaging studies of emotional memory in schizophrenia. There have however been a small number of studies that have investigated the neural correlates of viewing emotional scenes in patients and control subjects. Some of these studies have shown decreased amygdala activation to emotional scenes in patients with schizophrenia compared to controls (Paradiso et al., 2003; Takahashi et al., 2004), but others have not (Fahim et al., 2005; Taylor et al., 2002; Taylor et al., 2005). None of these studies have related amygdala activation to later memory for the scenes and as such little can be concluded from these results regarding the role of the amygdala in modulating emotional memory in schizophrenia.

1.5.4 Pavlovian fear conditioning

There have been remarkably few studies of Pavlovian fear conditioning in schizophrenia. Whilst this may in part reflect the aversive nature of the stimuli required for conditioning, human studies have been conducted using mildly aversive fear conditioning stimuli which could be adapted for patient populations (Buchel et al., 1998). In the only direct study of Pavlovian fear conditioning in schizophrenia published in the last 40 years Ax and colleagues, drawing upon an older Russian literature, demonstrated a marked impairment in the generation of conditioned skin conductance responses following association of a tone CS with a US of mild electric shock (Ax et al., 1970), results that are very similar to those seen following amygdala damage (LaBar et al., 1995). These studies were conducted in unmedicated patients with schizophrenia and the deficits in conditioned responding could not be accounted for in terms of differences in baseline responses to the conditioning stimuli. Although no further studies of Pavlovian fear conditioning have been conducted to substantiate these early findings, one study has
shown deficits in a subgroup of patients with early onset of illness in a related aversive avoidance conditioning procedure (Kosmidis et al., 1999). There have been no functional neuroimaging studies of Pavlovian fear conditioning in schizophrenia.

In summary therefore there have been very few studies of Pavlovian fear conditioning in schizophrenia. The available evidence is however consistent with abnormal amygdala function in schizophrenia.
1.6 Summary and hypotheses

Studies in primates and other mammals have highlighted a role for the amygdala in emotional and social processing. The identification of human subjects with selective amygdala damage has led to the development of a number of neuropsychological tests of amygdala function in humans which have been validated in both lesion and functional neuroimaging studies.

Structural studies of patients with schizophrenia have shown reductions in amygdala volume which have been replicated across a large number of studies. These abnormalities are also seen in the unaffected relatives of individuals with schizophrenia, suggesting that they represent a heritable vulnerability state for the disorder.

A key issue outstanding is whether these subtle but replicable abnormalities in amygdala structure in schizophrenia result in impairments in amygdala function. Investigation of amygdala function using neuropsychological tests in schizophrenia has so far been largely restricted to tests of facial affect recognition, in which a general impairment in facial affect recognition has been found, although with much heterogeneity between studies. Greater support for a functional impairment of the amygdala in schizophrenia would be provided if deficits were also found in other tasks known to depend on amygdala function.

In this thesis I investigated amygdala function in schizophrenia using three neuropsychological tests: i) facial affect recognition ii) social cognition and iii) emotional memory formation. In each case tests have been used that relate directly to those in which a role for the amygdala has been substantiated in both lesion and functional neuroimaging studies. We specifically hypothesised that individuals with schizophrenia would show the following deficits consistent with impaired amygdala function:
1. Impairments in interpreting facial emotions, particularly that of fear.

2. Impairments in tests of social cognition, particularly judgements of approachability and trustworthiness.

3. Decreased emotional enhancement of episodic memory for scenes, especially in delayed testing.
METHODS
2.1 Overview

Two experimental studies were conducted in this thesis. In the first (Study 1) the performance of patients with schizophrenia on tests of emotion recognition and social judgement from faces was assessed. In the second (Study 2) performance of subjects with schizophrenia on tests of the emotional enhancement of episodic memory for scenes was investigated. The methods used in these two studies are described in turn below.
2.2 Study 1: Facial emotion recognition and social cognition

2.2.1 Participants

Ethical approval for the study was obtained from the Lothian Research Ethics Committee. Participants were given a complete description of the study, and their written consent was obtained. No payment was given to subjects other than travel expenses.

Twenty patients meeting DSM-IV diagnostic criteria for schizophrenia participated in the study (APA 1994) and these were recruited from both inpatient and outpatient populations. Ten were men and ten were women; mean age was 33.4 years (SD 12.3), mean illness duration was 11.6 years (SD 8.8) and mean pre-morbid IQ (Nelson et al., 1982) was 111.1 (SD 8.1). All patients were Caucasian, 19 were right handed and 1 was left handed. All were treated with antipsychotic medication with a mean chlorpromazine equivalent dose of 467.5mg (SD 330). Symptoms were rated prior to testing using the positive and negative symptoms scale (PANSS) by a single clinician (JH) (Kay et al., 1987). Mean PANSS score was 51.6 (SD 14.5). Exclusion criteria were age under 18 or over 65, organic brain disease, dependence on alcohol or non-prescribed drugs and major psychiatric disorder other than schizophrenia.

Healthy controls were recruited from hospital staff, local industries and other volunteers. Ten were men and ten were women; mean age was 35.3 years (SD 11.4), and mean IQ was 113.8 (SD 6.2) (Table 1). All control subjects were Caucasian, 19 were right handed and 1 was left handed. Control subjects were screened for any family or personal history of psychiatric illness and were additionally subject to the same exclusion criteria as the patients.
2.2.2 Control tasks and facial identity recognition

Basic visual processing was assessed in all participants using the Vistech VCTS 6000 contrast sensitivity chart. To provide a more specific test of the subjects’ ability to process information regarding faces, and in particular facial identity, the Benton Test of Facial Recognition (Benton et al., 1983) was given. In this test, subjects have to choose which of six photographs of unfamiliar faces are pictures of the same person as a simultaneously presented target face photograph. The test includes items involving choice of identical photographs, as well as transformations of orientation or lighting, which are pooled to give an overall total score.

2.2.3 Tests of facial emotion recognition

Tests of facial emotion recognition were identical to those described in previous studies (Sprengelmeyer et al., 1996; Sprengelmeyer et al., 1999). Two tests were given: the Ekman 60 Faces test and the Megamix test. These are described briefly below.

(i) Ekman 60 Faces test - Recognition of prototypical facial expressions

Photographs of the faces of 10 people used in this test were taken from the Ekman and Friesen series (Ekman and Friesen, 1976). For each face, there were poses corresponding to each of 6 basic emotions (happiness, surprise, fear, sadness, disgust, and anger), giving a total of 60 photographs (10 for each emotion). These were shown one at a time on a computer screen in pseudo-random order, for 3 seconds each. The task involved deciding which of the emotion names (happiness, surprise, fear, sadness, disgust, or anger) best described the facial expression shown. All subjects were asked if they understood the
meanings of the emotional names, and if not brief standardised descriptions were given. The names of the six emotions were displayed at the bottom of the screen and they could be consulted throughout the test. The order of the emotions on the screen was varied between tests. Responses were made by clicking the computer mouse over the name of the selected emotion. There was no time limit for responding. The next face was not shown until the subject had made a response. No feedback was given as to the appropriateness of any responses.

(ii) Megamix

To provide a more stringent test of facial emotion recognition, and to corroborate the results from the Ekman 60 Faces test, we also conducted a test of facial emotion recognition using images morphed by shape. A set of facial expressions taken from the Ekman and Friesen (Ekman and Friesen, 1976) were ordered by placing each adjacent to the one it was most likely to be confused with; this gave the sequence happiness - surprise - fear - sadness - disgust - anger. The ends of this sequence (anger and happiness) were then joined to create a hexagon, and interpolated ('morphed') images representing 90%, 70%, 50%, 30% and 10% morphs between the two adjacent emotions were created for each emotion pair, generating a total of 30 morphed faces. These morphed faces were presented one at a time on a computer screen in random order for 3 seconds each. The task was to decide whether the image presented was most like happiness, surprise, fear, sadness, disgust, or anger. Responses were made using the computer mouse, with the names of the six possible emotions being displayed at the bottom of the screen which could be consulted throughout the test. There was no time limit for responding. No feedback was given as to the appropriateness of any responses. There were 6 blocks of trials. In each of these blocks of trials, all of the 30 morphed faces
were presented once. The first block was discounted as practice, and data from the remaining 5 blocks were used for analysis. Data from the 50% morphs was not included in the analysis, as the images were ambiguous, leaving a maximum of 20 correct responses for each emotion.

One subject from the Schizophrenic group was unable to complete the Megamix task and one set of control data for this task was lost due to computer error, leaving 19 in each group.

2.2.4 Tests of social cognition

A novel test of social cognition using faces developed by Dr I Santos and Professor A.W Young of the University of York and Dr R Sprengelmeyer of the University of St Andrews was utilised. The task was developed as follows. Five hundred pictures of faces derived from media sources, all of non-famous adults, were shown to six volunteer participants and were rated on six social dimensions on a scale of 1-7. The end-points of each scale were, respectively, young or old; very untrustworthy or very trustworthy; very unattractive or very attractive; very typical or very distinctive; very unintelligent or very intelligent; very unapproachable or very approachable. The faces were highly reliably related on each dimension across all raters (P<0.01). For each dimension, 32 faces were selected, comprising 16 faces representative of each valence (for example 16 “old” and 16 “young” faces), and these were used to construct the final test. The sets of faces for each social dimension were matched as closely as possible on the remaining five dimensions included in the test. Six practice sets of faces were also selected, which included 4 faces of each valence for the respective dimension.
In the test series used in the present study participants were shown 6 sets of 40 faces, with each set to be judged on one of the social dimensions (such as “very approachable” or “very unapproachable”). For each test participants were told that the faces had been chosen for the task such that half of them should be in each category. Faces were shown for 3 seconds each, and the alternative response choices were shown on the screen. Participants reported their choice to the experimenter, and the next picture was not shown until a response had been made. Participants were given 8 practice presentations (4 of each category) and if they showed a bias in responding they were again reminded that the faces had been selected such that half should be in each category. They were then asked to judge the remaining 32 faces in each dimension. No feedback was given as to the appropriateness of any of the individual responses. Responses were scored according to their agreement with the response most commonly selected in the pilot study, giving a maximum score of 32, with chance responding yielding a score of 16.

One participant in the schizophrenic group was unwilling to complete the trustworthiness and distinctiveness tests, but otherwise data were complete.

2.2.5 Data analysis

Statistical tests were performed using SPSS for Windows (version 12.0, SPSS Inc., US). Analysis of variance (ANOVA) was used to test for differences between groups.

As previous studies have suggested that the presence of acute, positive symptoms may influence performance on facial emotion recognition tasks (Gessler et al., 1989; Kohler et al., 2000) analyses were performed with the schizophrenic group subdivided into two groups according to the presence or absence of positive symptoms. Subjects
were placed in the positive symptom group (S-POS) if they scored 4 or more on any of the PANSS positive symptom categories (n=11, 6 male and 5 female) and were otherwise placed in the without positive symptoms (S-NOPPOS) group (n=9, 4 male and 5 female). The Bonferroni correction was applied where post-hoc comparisons between groups were made.

Individual subtests within the Ekman 60, Megamix and Social Cognition tests were analysed by one-way ANOVAs. For the Ekman 60 and Megamix tests of facial emotion recognition, results were considered significant overall only if a deficit was found in the same emotion on both tests, providing a conservative test of significance (P<0.0025). For the individual Social Cognition tests, where no second test was available, only results surviving Bonferroni correction for multiple comparisons were considered significant.
2.3 Study 2: Emotional memory

2.3.1 Participants

Ethical approval for the study was obtained from the Lothian Research Ethics Committee. Participants were given a complete description of the study, and their written consent was obtained. No payment was given to subjects other than travel expenses.

Twenty subjects with schizophrenia participated in the study, including both outpatients (13) and stable inpatients (7). Diagnosis was established on clinical consensus, based on DSM IV criteria (APA, 1994). Thirteen were men and seven were women; mean age was 34.5 years (SD 11.5); mean illness duration was 12.8 years (SD 8.8) and mean pre-morbid IQ assessed by the National Adult Reading Test (NART) (Nelson and Willison, 1991) was 110.9 (SD 8.8). All patients were treated with antipsychotic medication with a mean chlorpromazine equivalent dose of 597.5mg (SD 456.0) per day (BMA, 2006; Woods, 2003). In total 10 subjects were receiving atypical antipsychotics, 7 subjects were receiving typical antipsychotics and 3 subjects were receiving both. In addition 8 subjects were receiving antidepressants, 7 subjects were receiving anti-cholinergic mediation and 5 subjects were receiving benzodiazepines. Symptoms were rated prior to testing using the positive and negative syndrome scale (PANSS) (Kay et al., 1987) by a single clinician (JH) and the mean PANSS total score was 48.2 (SD 14.1). Exclusion criteria were age under 18 or over 65, co-morbid neurological conditions or brain injury, dependence on alcohol or non-prescribed drugs and major psychiatric disorder other than schizophrenia.

Matched healthy controls were recruited from hospital nursing and auxiliary staff, local industries and other volunteers. Thirteen were men and seven were women. They
were of mean age 35.5 years (SD 11.1) and had a mean NART IQ of 114.0 (SD 6.5). Control subjects were screened for any family or personal history of psychotic illness and were additionally subject to the same exclusion criteria as the patients.

2.3.2 Tests of emotional memory

A test of emotional enhancement of episodic memory was developed using pictures from the International Affective Picture System (Lang et al., 1997; Hall unpublished data). One hundred and twenty pictures were selected for the initial (encoding) phase of the study, of which 60 depicted emotionally neutral scenes, 30 depicted positive emotional scenes and 30 depicted negative emotional scenes. The mean normative control ratings for emotional valence (scored from 1 most negative to 9 most positive) and emotional arousal (scored from 1 minimum to 9 maximum) for these scenes was: neutral pictures valence 4.9 (SD 0.5), arousal 3.1 (SD 0.7); negative pictures valence 2.5 (SD 0.7), arousal 6.5 (SD 0.5) and positive pictures valence 7.1 (SD 0.6), arousal 5.7 (SD 0.8). A further group of 120 matched pictures was selected as distractors for the recognition memory test (mean normative population ratings neutral pictures valence 5.0 (SD 0.6), arousal 3.4 (SD 0.7); negative pictures valence 2.4 (SD 0.6), arousal 6.2 (SD 0.6); positive pictures valence 7.1 (SD 0.7), arousal 5.6 (SD 0.8)). Pictures were the same for male and female subjects except for 4 positive pictures per set with erotic content. For these, individuals viewed images of people to whom they were presumed to have a sexual attraction (the participant's sexual orientation having been discussed in the screening interview). All slides were presented on a PC using E-Prime software (Psychology Software Tools).
Subjects performed an incidental encoding task in which they were told that they would view a series of slides on a computer screen and would be required to rate the pictures according to how emotionally arousing they found them at the time. Arousal ratings have previously been shown to predict both immediate and delayed recall (Bradley et al., 1992). Subjects were instructed in rating pictures for arousal using a semantic differential scale based on the Self-Assessment Manikin system (Lang et al., 1997). Slides were rated from 1 (not at all arousing) to 9 (extremely arousing). After an initial three practice slides subjects were required to rate the full set of 120 slides in random order. To help counteract possible primacy and recency effects, two additional images were shown at the beginning and end of each 120 randomized image sequence. The ratings for these 4 images were discarded. Altogether, 4 picture sequences were used: two sets of randomized sequences for each gender, counterbalanced across groups. Each slide was shown on the screen for 6 seconds with a 15 second inter-slide interval (ISI) for rating. Participants were instructed to view each slide for the entire time it was on the screen prior to rating. Five seconds prior to the end of the ISI subjects were prompted on the screen to prepare to rate the next slide.

Subjects subsequently undertook surprise tests of both recall and recognition memory for the slides they had viewed. Recall was first tested 10 minutes after presentation of the slides (following an intervening distractor task which required completion of a personality questionnaire). Participants were required to write down a short description of as many slides as they could remember in 5 minutes, with sufficient detail for the investigator to be able to identify the specific slide. Pilot experiments had established that this was a sufficient period for subjects to have finished writing descriptions of all the slides they could recall. A further surprise recall test, using the same procedure, was conducted 3 weeks later.
Recognition memory for the slides was tested after the second recall test (3 weeks after initial presentation of the slides). Subjects were shown all 120 slides they had seen previously together with the 120 distractor slides in random order. Participants were required to make one of two keyboard responses depending on whether they recognised the slide or not (1=recognised, 2=not recognised) and responses were collected and scored using E-prime software (Psychology Software Tools).

Complete data were available for all participants with the exception of one control subject who was not available for the delayed recall and recognition tests due to illness.

2.3.3 Data analysis

The arousal ratings of each slide were determined from subjects’ responses and a mean rating for each emotional category (negative, neutral and positive) was calculated for each subject. Comparisons between groups and emotional categories were made on the basis of these mean scores.

Recognition memory was calculated using a recognition accuracy measure which accounts for both the rate of correct responses on the previously seen slides (hit rate, given as the number of old slides correctly identified as seen before divided by the total number of old slides) and the rate of incorrect responses on the distractor slides (false alarm rate, given as the number of distractor slides incorrectly identified as old divided by the total number of distractor slides) (Macmillan and Creelman, 1991; Richardson et al., 2004). Recognition accuracy was calculated as the difference between the hit rate and the false alarm rate and has maximum value +1 (perfect identification of stimuli present at encoding) and minimum value -1 (perfect identification of distractors).
Recognition accuracy scores were calculated for each subject for each emotional category (negative, neutral and positive). The emotional enhancement of recognition memory was further assessed by calculating the difference in recognition accuracy between the emotional slides (negative and positive) and neutral slides for each subject.

Recall memory was assessed by a rater who was blind to the subjects’ group allocation. Where the information given was too limited to identify a slide no score was given. Where a group of slides was identified in a single statement only one slide was scored. The percentage of slides recalled in each category (negative, neutral and positive) was calculated for each subject for use in subsequent analysis. Emotional enhancement of memory was specifically investigated by calculating the difference in recall between the emotional slides (negative and positive) and neutral slides for each subject.

We hypothesised that effects on recall memory may be selectively seen for the most emotional stimuli (Canli et al., 2000). We therefore performed a secondary analysis of recall memory for the 15 most emotionally arousing slides from each emotional category (negative or positive), as rated by population controls.

Statistical tests were performed using SPSS for Windows (version 12.0, SPSS Inc., US). Analysis of variance (ANOVA) was used to test for differences between groups. For analysis of the slide rating and memory data repeated measures ANOVA’s were conducted with Group (control or schizophrenia) as a between subjects variable and Stimulus (negative, neutral or positive slides) as a within subjects variable. Where group or stimulus effects were detected the source of these effects was further investigated using post-hoc t-tests. Post-hoc tests were made only to investigate our specific a priori hypothesis that subjects with schizophrenia have impairments in emotional memory and therefore the Bonferroni correction was not applied.
RESULTS
3.1 Study 1: Facial emotion recognition and social cognition

3.1.1 Demographic variables

There were no differences between the schizophrenic and control groups in terms of age (F_{1,38}=0.2, P=0.6) or NART IQ (F_{1,38}=1.4, P=0.2) (Table 3.1). All subjects achieved at least 20/30 vision on the Vistech VCTS 6000 contrast sensitivity chart. Notably, even when the schizophrenic group was subdivided according to the presence or absence of positive symptoms there was still no significant difference between groups in terms of demographic variables (for age, F_{2,37}=1.9, P=0.2; for IQ, F_{2,37}=1.3, P=0.3).
<table>
<thead>
<tr>
<th></th>
<th>Age (mean)</th>
<th>Number (M:F)</th>
<th>NART IQ (mean)</th>
<th>Benton (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenic group</td>
<td>33.4</td>
<td>20 (10:10)</td>
<td>111.1</td>
<td>46.8</td>
</tr>
<tr>
<td>Control group</td>
<td>35.3</td>
<td>20 (10:10)</td>
<td>113.8</td>
<td>46.9</td>
</tr>
</tbody>
</table>

Table 3.1  Demographic information and performance on Benton Facial Recognition task for subjects in Study 1.
3.1.2 Facial identity recognition

There was no difference between groups in terms of their performance on the Benton test of Facial Recognition ($F_{1,38}=0.02$, $P=0.9$) (Table 3.1). In addition there was no difference between the S-POS and S-NOPOS groups in facial identity recognition, with both groups showing equal performance to control subjects ($F_{2,37}=1.3$, $P=0.9$) (Figure 3.1).
Figure 3.1 Overall performance of controls (CON), schizophrenics with positive symptoms (S-POS) and schizophrenics without positive symptoms (S-NOPOS) on tests of facial identity recognition (Benton), facial emotion recognition (Ekman 60 and Megamix) and social judgement from faces (Social Cognition). Bars show mean number of correct responses for each test, expressed as a percentage of the level of correct responding in the control group. Error bars represent standard error of the mean.
3.1.3 Facial emotion recognition

The overall performance of control and schizophrenic subjects on the Ekman 60 and Megamix tests of facial emotion recognition was initially investigated. Subjects with schizophrenia showed a significant overall deficit on facial emotion recognition on both the Ekman 60 ($F_{1,38}=5.7$, $P=<0.05$) and Megamix ($F_{1,38}=4.2$, $P<0.05$) tests.

As previous studies had demonstrated a differential deficit in emotion recognition in patients experiencing acute positive symptoms (Gessler et al. 1989; Kohler et al. 2000) the difference in performance of patients with and without positive symptoms was next examined by performing one-way ANOVA’s with Controls, S-POS and S-NOPOS as groups. There were significant effects of group on the Ekman 60 ($F_{2,37}=6.1$, $P<0.01$) and Megamix ($F_{2,35}=7.3$, $P<0.01$) test which post-hoc comparisons showed derived from a significant deficit in the S-POS group ($P<0.01$), but not the S-NOPOS group ($P>0.9$), relative to controls (Figure 3.1). Due to this specific deficit in the S-POS group, subsequent analyses were performed using the S-POS, S-NOPOS and Control groups.

The performance of subjects across the six different emotions presented in each test was next investigated. Repeated measures ANOVAs with group (Control, S-POS, S-NOPOS) as a between-subjects factor and stimulus (emotion tested) as a within-subjects factor showed significant effects of group and stimulus on both the Ekman 60 ($F_{2,37}=6.1$, $P<0.01$, and $F_{4,137}=24.2$, $P<0.001$) and Megamix ($F_{2,35}=7.3$, $P<0.01$, and $F_{3,106}=3.0$, $P=0.01$) tests, as well as significant group by stimulus interactions for both tests ($F_{7,137}=2.6$, $P<0.05$, and $F_{6,106}=2.3$, $P<0.05$ respectively) (Figure 3.2). Post-hoc comparisons confirmed that the group effect derived from poorer performance in the S-POS group ($p<0.01$). Analysis of individual tests showed deficits in fear and happiness.
recognition in the S-POS group in both the Ekman 60 and Megamix, and also deficits in the S-POS groups compared to the S-NOPOS group on both tests in disgust recognition (see Table 3.2).
<table>
<thead>
<tr>
<th></th>
<th>S-POS (1)</th>
<th>S-NOPOS (2)</th>
<th>CON (3)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ekman 60 Faces Test (max score = 10)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>6.2 (3.0)</td>
<td>7.3 (2.1)</td>
<td>7.9 (1.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Disgust</td>
<td>5.0 (3.5)</td>
<td>8.6 (1.6)</td>
<td>7.5 (2.5)</td>
<td>p&lt;0.05 (1&lt;2,3)</td>
</tr>
<tr>
<td>Fear</td>
<td>4.7 (1.8)</td>
<td>6.6 (1.7)</td>
<td>6.6 (1.9)</td>
<td>p&lt;0.05 (1&lt;3)</td>
</tr>
<tr>
<td>Happiness</td>
<td>9.1 (1.5)</td>
<td>9.9 (0.3)</td>
<td>10.0 (0)</td>
<td>p&lt;0.05 (1&lt;3)</td>
</tr>
<tr>
<td>Sadness</td>
<td>6.9 (2.3)</td>
<td>8.7 (1.6)</td>
<td>8.4 (1.1)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Surprise</td>
<td>8.4 (1.8)</td>
<td>7.3 (2.1)</td>
<td>9.2 (1.0)</td>
<td>p&lt;0.05 (2&lt;3)</td>
</tr>
<tr>
<td><strong>Megamix (max score = 20)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>13.0 (7.4)</td>
<td>18.0 (1.8)</td>
<td>17.3 (1.3)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Disgust</td>
<td>11.1 (8.3)</td>
<td>19.0 (1.3)</td>
<td>14.9 (6.3)</td>
<td>p&lt;0.05 (1&lt;2)</td>
</tr>
<tr>
<td>Fear</td>
<td>12.4 (5.8)</td>
<td>17.9 (2.3)</td>
<td>17.9 (1.9)</td>
<td>p&lt;0.001 (1&lt;2,3)</td>
</tr>
<tr>
<td>Happiness</td>
<td>15.7 (6.5)</td>
<td>19.9 (0.3)</td>
<td>20.0 (0)</td>
<td>p&lt;0.01 (1&lt;2,3)</td>
</tr>
<tr>
<td>Sadness</td>
<td>16.8 (5.0)</td>
<td>18.9 (2.1)</td>
<td>19.3 (1.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Surprise</td>
<td>14.8 (6.2)</td>
<td>14.4 (5.1)</td>
<td>18.7 (2.1)</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

**Table 3.2** Identification of emotion in facial expressions (Ekman 60 Faces test and Megamix test) by patients with schizophrenia and active positive symptoms (S-POS), those with schizophrenia without positive symptoms (S-NOPOS) and those in the control group (CON). Mean score (SD). Levels of significance on one-way ANOVA and post-hoc comparisons (P<0.05) are shown for each test, ns = not significant.
Figure 3.2 Performance of schizophrenic patients and control subjects on tests of facial emotion recognition on the a) Ekman 60 test b) Megamix test, with schizophrenic patients subdivided by presence or absence of positive symptoms. ANG = anger, DIS = disgust, FEAR = fear, HAP = happiness, SAD = sadness, SUR = surprise. CON = controls, S-POS = schizophrenic patients with positive symptoms, S-NOPOS = schizophrenic patients without positive symptoms. Bars show mean number of correct responses for each emotion. Error bars represent standard error of the mean.
3.1.4 Social cognition

Analysis of the overall performance of schizophrenic and control subjects on the social cognition tests revealed a highly significant effect of group (F_{1,38}=34.7, P<0.001; effect size as standardised difference = 2.3), characterised by a deficit in performance in the schizophrenic group. One-way ANOVA’s with Controls, S-POS and S-NOPOS as groups were next performed to assess whether there was any difference in performance on the social cognition tests between schizophrenic subjects with or without acute positive symptoms. This revealed a significant overall effect of group (F_{2,37}=17.2, P<0.001). Post-hoc analysis demonstrated that, in contrast to the results seen for facial emotion recognition, this effect derived from deficits in both the S-POS and S-NOPOS groups relative to Controls (P<0.001 in both cases; Figure 3.1). Furthermore there was no difference between the S-POS and S-NOPOS groups (P=1.0) in performance on the social cognition tests. As there was no difference between the S-POS and S-NOPOS groups these were combined as a single schizophrenic group for all further analyses.

The performance of the schizophrenic and control groups across the 6 individual tests of social cognition was examined using a repeated measures ANOVA, with group (Control and Schizophrenic) as a between-subjects factor and stimulus (social test) as a within-subjects factor. This revealed significant effects of both group (F_{1,38}=34.7, P<0.001) and stimulus (F_{3,129}=21.7, P<0.001) and a significant group by stimulus interaction (F_{3,129}=4.0, P<0.01) (Figure 3.3). One-way ANOVAs were performed to examine the relative performance of schizophrenic and control subjects on the individual tests within the social cognition battery (Table 3.3), and significant effects for judgements of approachability (P<0.001), intelligence (P<0.001) and distinctiveness (P<0.05) survived Bonferroni correction for multiple comparisons.
<table>
<thead>
<tr>
<th></th>
<th>SCH</th>
<th>CON</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(max score = 32)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>29.7 (1.2)</td>
<td>30.9 (2.1)</td>
<td>p&lt;0.05</td>
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<tr>
<td>Trustworthiness</td>
<td>24.3 (3.3)</td>
<td>25.2 (3.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Attractiveness</td>
<td>24.7 (3.9)</td>
<td>26.7 (3.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Distinctiveness</td>
<td>21.2 (5.2)</td>
<td>24.4 (3.7)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Intelligence</td>
<td>22.7 (3.6)</td>
<td>27.8 (2.3)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Approachability</td>
<td>23.9 (5.1)</td>
<td>29.4 (3.1)</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 3.3**  Social Cognition scores of patients with schizophrenia (SCHIZ) and controls group (CON). Mean score (SD). Levels of significance on one-way ANOVA are shown for each test, ns = not significant.
Figure 3.3  Performance of schizophrenic patients and control subjects on tests of social judgement from faces. AGE = age test, TRU = trustworthiness test, ATT = attractiveness test, DIS = distinctiveness test, INT = intelligence test, APP = approachability test. CON = controls, SCH = schizophrenic patients. Bars show mean number of correct responses for each test; chance level of responding = 16. Error bars represent standard error of the mean.
3.1.5 Control variables and correlations

To confirm that the observed effects on facial emotion recognition and social judgement could not be accounted for by variations between participants in age, gender, IQ, dose of antipsychotic, duration of illness or facial recognition ability *per se* (as assessed by the Benton test) correlation analysis was performed for all variables for which significant effects were found. No significant correlations were found for age, gender, dose of antipsychotic, duration of illness or facial recognition. Happiness judgements on the Megamix and Intelligence judgements in the Social Cognition tests were found to covary with IQ, but none of these effects survived correction for multiple comparisons.

Further analysis was undertaken to determine whether the impairments in social cognition seen in schizophrenic patients could be accounted for by their deficits in facial emotion recognition. Analysis of covariance (ANCOVA) was performed for the social cognition tests with scores on the facial emotion recognition tests as covariates, and the effect of schizophrenia on social judgement overall and on approachability, intelligence and distinctiveness judgements was found to remain significant when Faces 60 scores, Megamix scores or combined scores were used as covariates (P<0.05 in all cases).
3.2 Study 2: Emotional memory

3.2.1 Demographic variables

There were no differences between subjects with schizophrenia and control subjects in terms of age ($F_{1,38}=0.1$, $P=0.8$) or NART IQ ($F_{1,38}=1.6$, $P=0.2$) (Table 3.4).
<table>
<thead>
<tr>
<th></th>
<th>Age (mean)</th>
<th>Number (M:F)</th>
<th>NART IQ (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenic group</td>
<td>34.5</td>
<td>20 (13:7)</td>
<td>110.9</td>
</tr>
<tr>
<td>Control group</td>
<td>35.5</td>
<td>20 (13:7)</td>
<td>114.0</td>
</tr>
</tbody>
</table>

**Table 3.4**  Demographic information and performance of subjects participating in Study 2.
3.2.2 Slide ratings

Both groups rated the emotional slides (negative and positive) as more arousing than the neutral slides as demonstrated by a main effect of stimulus ($F_{2,76}=107.1$, $P<0.001$) (Figure 3.4). There was no difference between groups in their rating of the slides ($F_{1,38}=0.8$, $P=0.4$) and no group by stimulus interaction ($F_{2,76}=1.4$, $P=0.25$). Post-hoc t-tests confirmed that both patients and controls rated the positive and negative emotional scenes as more arousing than neutral scenes ($P<0.001$ for all), and that patients and control subjects did not differ in their ratings of any of the stimulus categories ($P>0.1$ in all cases).
Figure 3.4. Mean ratings of emotional arousal for the negative (Neg), neutral (Neu) and positive (Pos) slides. CON = control group. SCH = schizophrenia group. Error bars represent standard error of the mean.
3.2.3 Recognition

Patients with schizophrenia showed a selective deficit in the recognition of emotional scenes compared to control subjects (Figure 3.5). This was revealed as a significant group by stimulus interaction ($F_{2,74}=3.2$, $P<0.05$). Post-hoc t-tests showed that this effect was characterised by impaired recognition in the schizophrenia group of both negative ($T=2.6$, $P<0.05$) and positive ($T=3.0$, $P<0.01$) scenes, but not of neutral scenes ($T=1.4$, $P=0.18$). Control subjects showed a significant enhancement in recognition memory for both positive and negative scenes ($P<0.05$ in both cases), which was absent in patients with schizophrenia ($P>0.6$ in both cases). Measures of emotional enhancement, which account for differences between groups in baseline memory, confirmed a deficit in patients compared to controls for both negative ($F_{1,37}=4.8$, $P<0.05$) and positive ($F_{1,37}=7.6$, $P<0.01$) scenes (Figure 3.5). Of note these group effects could not be explained by any overall bias in response tendency ($F_{1,37}=0.08$, $P=0.8$).

As differences between subjects experiencing positive symptoms and those without such symptoms had been noted in the tests of facial emotion recognition the effect of symptom status on recognition memory was examined. There was no difference in recognition memory performance or emotional enhancement of recognition memory between those subjects with positive symptoms (scoring 4 or more on the PANSS, $n=7$) and those without positive symptoms ($P>0.8$ in both cases).
Figure 3.5 Recognition memory. a) Mean recognition accuracy for the negative (Neg), neutral (Neu) and positive (Pos) slides. A recognition accuracy score of +1 indicates perfect identification of stimuli seen at encoding; -1 indicates perfect recognition of distractors. b) Mean emotional enhancement in recognition accuracy above that for neutral slides for the negative (Neg) and positive (Pos) slides. CON = control group. SCH = schizophrenia group. Error bars represent standard error of the mean.
3.2.4 Recall

In the tests of memory recall patients with schizophrenia had worse overall memory than control subjects at both time points (Figure 3.6). Analysis of performance at the 10 minute recall test demonstrated a significant effect of stimulus (F_{2,76}=36.8, P<0.001) and a significant effect of group (F_{138}=5.2, P<0.05), but no group by stimulus interaction (F_{2,76}=0.4 P<0.69). The same pattern was seen at the 3 week recall test with a main effect of both stimulus (F_{2,74}=24.1, P<0.001) and group (F_{1,37}=6.3, P<0.05) but no group by stimulus interaction (F_{2,74}=0.7, P<0.50). Planned t-contrasts confirmed that patients and controls showed an enhancement of recall memory for the emotional scenes relative to the neutral scenes (P<0.05 in all cases). Post-hoc tests further revealed that patients were impaired relative to controls on the recall of negative and neutral scenes at the 10 minute and 3 week tests (P<0.05 in all cases) but were not impaired in either test on the recall of positive stimuli (P>0.3 for both).

A secondary analysis was performed to determine whether subjects with schizophrenia had a selective deficit in memory enhancement for the most arousing emotional scenes. This showed that patients with schizophrenia have a deficit in memory for the most emotionally arousing negative scenes compared to controls at both the 10 minute (F_{1,38}=8.5, P<0.01) and 3 week tests (F_{1,37}=20.4, P<0.001), that was absent for the less arousing negative scenes (F_{1,38}=0.2, P<0.66 and F_{1,37}=0.50, P=0.48 respectively) (Figure 3.7). No such difference between groups was apparent for positive scenes. Measures of emotional enhancement, which assess the enhancement of memory for the most arousing emotional pictures over memory for the neutral stimuli, confirmed a trend to an effect of group at 10 minutes (F_{1,37}=3.3, P=0.08) and a significant effect of group at 3 weeks (F_{1,37}=8.1, P<0.01).
Further analysis revealed that there was no difference between subjects experiencing positive symptoms of greater than 4 on the PANSS and those without such symptoms on any measures of recall memory (P>0.7 in all cases).
Figure 3.6 Mean recall of the negative (Neg), neutral (Neu) and positive (Pos) slides at a) 10 minutes and b) 3 weeks. CON = control group. SCH = schizophrenia group. Error bars represent standard error of the mean.
Figure 3.7 Mean recall of the 15 most arousing negative slides (High Neg) compared to the 15 least arousing negative slides (Low Neg) at a) 10 minutes and b) 3 weeks. CON = control group. SCH = schizophrenia group. Error bars represent standard error of the mean.
3.2.5 Control variables and correlations

Correlations were investigated to test whether the memory performance of patients was related to their total medication dose, their symptom status as rated by the PANSS, or duration of illness. There were no significant correlations between any of the measures of memory and dose of antipsychotic medication. There were also no correlations between PANSS positive symptoms and PANSS general symptoms and memory performance. There were no significant correlations between memory measures and depression and anxiety ratings on the PANSS. There was however a significant correlation between PANSS negative symptoms and recall of neutral scenes at 10 minutes \((r=-0.6, P<0.01)\) and recognition memory for both negative \((r=-0.7, P=0.001)\) and neutral \((r=-0.5, P<0.05)\) scenes. In addition there was an effect of duration of illness on memory as demonstrated by correlations between years of illness and recall of neutral scenes at 10 minutes \((r=-0.5, P<0.05)\); recall of negative scenes at 3 weeks \((r=-0.5, P<0.05)\); recall of neutral scenes at 3 weeks \((r=-0.5, P<0.05)\); recognition of negative scenes \((r=-0.6, P<0.01)\), recognition of neutral scenes \((r=-0.6, P<0.01)\) and recognition of positive scenes \((r=-0.5, P<0.05)\).

The relationship between memory performance across the two groups and demographic variables including age and pre-morbid (NART) IQ was next investigated. No clear patterns emerged. Pre-morbid IQ was correlated with worse memory for neutral pictures and better memory for positive pictures at the 10 minute test \((r=-0.4, P<0.01\) and \(r=0.5, P<0.01\) respectively) but not with any of the other memory measures. Age was correlated with recognition memory for neutral pictures \((r=-0.4, P<0.05)\) but not with other measures. These isolated effects would not survive correction for the multiple comparisons made.
There were no significant correlations between the subjective slide arousal rating scores and medication dose, PANSS scores or number of years of illness, age, or premorbid IQ.
4.1 Summary of main findings

Two studies designed to test amygdala function in schizophrenia were conducted. The first study investigated the performance of subjects with schizophrenia on tests of facial emotion recognition and social cognition from faces. Subjects with schizophrenia were able to process general information about faces as demonstrated by intact performance on a test of facial identity recognition. However a state-dependent deficit was observed in facial emotion recognition, with subjects experiencing positive symptoms showing significantly impaired abilities to identify basic facial emotions. In addition, in tests of more complex social judgements from faces, patients with schizophrenia showed severe impairments whether or not they were experiencing positive symptoms.

The second study tested emotional memory formation in subjects with schizophrenia. Patients with schizophrenia showed a marked impairment in the emotional enhancement of recognition memory for scenes, despite preserved subjective ratings of the emotional content of the pictures. In addition individuals with schizophrenia were impaired in their overall ability to recall the scenes, with a selective impairment in recall of the most arousing negative scenes.

In the sections that follow the findings from the three tests of amygdala function conducted in these studies (facial emotion recognition, social cognition and emotional memory) are considered in turn. This is followed by a general discussion of the implications of these findings in terms of amygdala function in schizophrenia. Finally the strengths and limitations of the present studies are considered followed by a discussion of directions for future research.
4.2 Facial emotion recognition

In the present study individuals with schizophrenia who were experiencing positive symptoms showed marked deficits in their ability to recognise the emotion of fear from faces. This deficit is similar to that shown by subjects with amygdala lesions and therefore supports the view that amygdala function is abnormal in patients with schizophrenia, at least during psychotic episodes (Adolphs et al., 1994; Adolphs et al., 1999; Evangeli and Broks, 2000). Impaired recognition of fear in subjects with positive symptoms was seen in both the tests of facial emotion recognition conducted, providing evidence for the internal consistency of these findings.

The deficits in facial emotion processing seen in subjects with schizophrenia with positive symptoms in the present study were not restricted to the emotion of fear. Whilst the largest and most consistent impairment was seen in fear recognition, more subtle deficits were apparent in the recognition of all the facial emotions (Table 3.2, Figure 3.2). This reflects the findings from studies of groups of individuals with amygdala lesions, which have also revealed subtle impairments in the recognition of a range of facial emotions (Adolphs et al., 1999). The view that the more general impairments in facial emotion processing seen in the present study derived from abnormal amygdala function is supported by the results of neuroimaging studies which have shown deficits in amygdala activation in patients with schizophrenia compared to control subjects when viewing a range of facial emotions (Gur et al., 2002; Johnston et al., 2005).

The present finding of selective deficits in facial emotion recognition in those experiencing positive symptoms may help explain some of the discrepancies seen between previous investigations of facial emotion recognition in schizophrenia. Only a minority of studies have compared patients with or without active positive symptoms
(Cutting et al., 1981; Gessler et al., 1989; Kohler et al., 2000; Mandal et al., 1998; Sachs et al., 2004; Weninger et al., 2004 Wolwer et al., 1996;), with the majority of studies that have made such a comparison identifying greater impairment in acutely psychotic individuals (Cutting et al., 1981; Gessler et al., 1989; Kohler et al., 2000; Mandal et al., 1998; Weninger et al., 2004). Given the selective deficits that we have found in those with positive symptoms, it is unsurprising that studies of patients with different (or mixed) clinical presentations may have produced apparently discrepant results. Previous studies have also employed a wide range of methodologies, often without looking at specific emotions (Edwards et al., 2002; Mandal et al., 1998). In contrast the present study used standardised test stimuli identical to those previously used to demonstrate impairments in patients with amygdala damage (Sprengelmeyer et al., 1999), enabling direct comparisons to the deficits seen following amygdala lesions to be made.

The current results raise the issue of why the deficits seen in emotion recognition are state-dependent, being limited to individuals experiencing positive symptoms. One explanation could be that the amygdala is subject to phasic functional impairments during psychotic episodes. Such an hypothesis is consistent with the observation that psychotic symptoms can accompany seizures which have a medial temporal lobe focus (Slater and Beard, 1963; Trimble and Van Elst, 2003). However an alternative possibility is that patients who are free of psychotic symptoms are able to use alternative cognitive strategies, not requiring the amygdala, to identify basic facial emotions. This view is supported by a recent fMRI study in which schizophrenic patients, none of whom were experiencing positive symptoms, were found to show deficits in amygdala activation during facial emotion processing, but did not show any deficits in identifying the emotions expressed (Gur et al., 2002). These authors suggested that enduring amygdala deficits might be revealed in tests of more complex social judgements, in which
compensatory processes are less likely to have developed. It is just such complex social judgements that were assessed in the tests of social cognition presented here.
4.3 Social cognition

Subjects with schizophrenia showed major deficits in their ability to make social judgements from faces. These findings could not simply be explained in terms of task difficulty, as patients showed marked impairments on tasks which control subjects performed with a high degree of accuracy, such as judgements of approachability. The amygdala has been shown to play a central role in social cognition in both lesion and neuroimaging studies (Adolphs 1998 et al.; Baron-Cohen et al., 1999; Winston et al., 2002) and the present results are therefore consistent with the view that amygdala function is abnormal in schizophrenia.

The current findings also support the more general hypothesis that impairments in the ability to attribute mental states to others (mentalising ability) may contribute to the symptoms of schizophrenia (Frith, 1992). Subjects with schizophrenia have been found to show deficits in mentalising ability in a range of tasks including the faux-pas and hinting tasks and tests using cartoons, pictures, stories and metaphors (Brune, 2005; Corcoran, 2001; Frith, 2004; Lee et al., 2004). This inability to judge the intentions of others may contribute to the symptoms of schizophrenia, such as paranoia and social withdrawal (Frith, 1992). Neuroimaging studies have shown that the ability to judge the mental state of others from faces requires a network of brain regions including the amygdala (Baron-Cohen et al., 1999; Winston et al., 2002). The present studies show that patients with schizophrenia are impaired in the performance of a range of tests of social judgement from faces, including those previously shown to depend upon the integrity of the amygdala (Adolphs et al., 1998; Winston et al., 2002), supporting the view that deficits in amygdala function may contribute to the impairments in mentalising ability seen in patients with schizophrenia.
Whilst the current results are consistent with abnormal amygdala function in schizophrenia, a number of issues remain to be addressed. Firstly, whilst large deficits were found in the patients performance in judgements of approachability, a task known to depend upon the amygdala, significant deficits were not seen in judgements of trustworthiness which is similarly dependent upon amygdala function (Adolphs et al., 1998; Winston et al., 2002). Secondly, deficits were also seen in tasks that have not previously been associated with amygdala function, such as judgements of intelligence from faces. Thirdly, the deficits observed in social cognition were seen in patients both with and without acute positive symptoms, in contrast to the impairments in facial emotion recognition. These issues are addressed in turn below.

The lack of significant deficits in the performance of patients in judgements of trustworthiness, in contrast to the large deficit seen in judgements of approachability, may have a number of explanations. Firstly the approachability test was performed highly accurately by control subjects in the present study and may therefore be a more sensitive test than the trustworthiness test on which control subjects performed much less reliably. The current study may have therefore been underpowered to detect a deficit in trustworthiness judgements using the current task. Notably subjects with schizophrenia did show a trend to a deficit in trustworthiness judgements, which failed to reach statistical significance. Secondly the tests of social judgement used in this study required individuals to make a dichotomous judgement (for example “very untrustworthy” or “very trustworthy”), whereas previous studies have used a likert scale to assess social ratings. The use of a dichotomous judgement may have obscured more subtle biases in social judgement, such as the tendency for subjects with amygdala damage to rate faces as more trustworthy than controls (Adolphs et al., 1998).
Marked deficits in social judgement were observed in subjects with schizophrenia in social tasks that have not previously been shown to depend upon amygdala function, such as judgements of intelligence from faces. Notably these tasks lack a clear emotional or threat-related component, which has previously been considered a key role for the amygdala in social judgement (Adolphs, 2001; Winston et al., 2002). However other studies have suggested a broader role for the amygdala in social cognition not restricted to decisions related to threat (Baron-Cohen et al., 1999; Fitzgerald et al., 2006). I, with colleagues, have directly addressed the issue of whether the amygdala is activated only during threat-related social judgements or plays a more general role in social cognition by using fMRI to investigate the patterns of brain activation that accompany the performance of the tasks used here (Hall et al. unpublished data). These studies have shown that both the approachability and intelligence tasks used in the present study produce activation of the amygdala compared to judgements of gender made from the same stimuli. This confirms that the amygdala is involved in both the social judgement tasks in the present study in which the greatest impairments were seen in subjects with schizophrenia and suggest a role for the amygdala in social judgement which extends beyond detecting threat alone. Performance of these social judgment tasks activated a network of brain regions which included the medial prefrontal cortex and superior temporal gyrus, supporting the view that the amygdala is part of a system of interacting brain regions recruited during the performance of complex social judgements (Adolphs, 2001; Amodio and Frith, 2006b; Brothers, 1990; Winston et al., 2002).

Impairments in social judgement in subjects with schizophrenia were evident whether or not the individual was experiencing positive symptoms as the time of testing. This suggests that impaired social cognition may represent a trait deficit in schizophrenia. Previous studies using videotaped or scripted interactions and role play have similarly
demonstrated stable impairments in social cognition in schizophrenia (reviewed in Penn et al., 1997), and impaired social cognition has been argued to represent a core deficit in schizophrenia (Burns, 2004). Patients with schizophrenia have been shown to have structural abnormalities in frontal and temporal lobe regions involved in social cognition that are not restricted to the amygdala, but also include the medial prefrontal cortex and superior temporal gyrus (Honea et al., 2005; Lawrie and Abukmeil, 1998; Wright et al., 2000). The marked and stable impairments in social cognition seen in the present study may therefore derive from the combined effect of dysfunction of several components of the fronto-temporal network required for social cognition (Burns, 2004).

Overall the present findings of marked impairments in social cognition are consistent with abnormalities in amygdala function in schizophrenia. The amygdala is only part of a network of brain regions involved in making such complex social judgements, which also includes the medial prefrontal cortex and superior temporal gyrus. It is likely that the severe and stable deficits in social cognition seen in individuals with schizophrenia represent not only abnormal amygdala function, but also a more general breakdown in the integration of frontal and temporal lobe regions required for social cognition.
4.4 Emotional memory

The present study demonstrated a significant impairment in the emotional enhancement of recognition memory for scenes in subjects with schizophrenia, despite preserved subjective ratings of the emotional content of the pictures. This pattern of results closely resembles that seen in individuals with amygdala damage (Adolphs et al., 1997; Cahill et al., 1995; Hamann et al., 1997), and therefore supports the view that patients with schizophrenia have impairments in amygdala function.

The finding that patients with schizophrenia reported normal subjective ratings of emotional arousal to the slides replicates the findings of a number of previous studies which have shown that patients rate emotion normally in pictures (Bigelow et al., 2006), words (Koh et al., 1976; Mathews and Barch 2004) and films (Earnst and Kring, 1999; Earnst et al., 1996; Kring et al., 1993; Kring and Neale, 1996). These results therefore suggest that patients with schizophrenia, like subjects with amygdala damage, are able to experience emotion normally, but have a deficit in the impact of emotion on memory (Adolphs et al., 1997; Cahill et al., 1995; Hamann et al., 1997).

Impairments in the emotional enhancement of recognition memory relate closely to the known function of the amygdala in memory modulation as previously investigated in functional neuroimaging studies. Activation of the amygdala has been shown in neuroimaging studies to correlate with enhanced subsequent recognition memory for emotional slide stimuli (Hamann et al., 1999; Canli et al., 2000), and also to correlate with increased hippocampal activation (Hamann et al., 1999; Richardson et al., 2004). These findings support the view that the amygdala enhances the consolidation of memories for emotional stimuli in medial temporal lobe memory systems (McGaugh, 2004). Imaging studies in patients with schizophrenia have previously shown decreased
amygdala activation to slide stimuli (Paradiso et al., 2003; Takahashi et al., 2004; Taylor et al., 2002), however these studies have not investigated the relationship between decreased amygdala activation and subsequent memory performance.

In addition to impaired emotional modulation of recognition memory patients also showed deficits in overall recall for both emotional and non-emotional stimuli. This is in keeping with previous findings that have demonstrated greater impairment in recall memory than recognition memory in schizophrenia (Bauman and Murray, 1968; Calev, 1984; Huron et al., 1995). The deficit in recall memory is likely to reflect a selective impairment in hippocampal function in schizophrenia. The hippocampus is required for the formation of episodic memories and evidence suggests that it plays a particular role in recollection based memory rather than familiarity based memory (Aggleton et al., 2005; Rugg and Yonelinas, 2003; Yonelinas, 2002). Hippocampal volume has been consistently shown to be reduced in schizophrenia (Lawrie and Abukmeil, 1998; Nelson et al., 1998; Wright et al., 2000). Furthermore a recent meta-analysis of functional imaging studies of episodic memory in schizophrenia has confirmed that patients show a relative hypo-activation of the hippocampus, but a preservation of activation in the parahippocampal gyrus, a region implicated in familiarity judgements and recognition memory (Achim and Lepage, 2005). Overall these finding are consistent with the view that the deficit in recall memory seen in the present study derives from impaired hippocampal function, although we cannot exclude the possibility that other cognitive impairments in the patient group, such as deficits in attention, may also have contributed to this finding.

Individuals with schizophrenia showed relatively intact emotional modulation of recall memory, however they did show a selective deficit in the enhancement of recall memory for the most arousing aversive stimuli. Imaging studies have shown that
amygdala activation at encoding is predictive of subsequent memory only for the most emotionally arousing scenes (Canli et al., 2000). In the present study the most arousing negative scenes were rated as more arousing than the positive scenes, reflecting the generally more arousing nature of negative stimulus material. The selective deficit in recall of the most arousing negative scenes may therefore derive from an impairment in amygdala-mediated enhancement of memory for the most emotionally arousing stimuli. The more subtle impairments in emotional memory formation seen in recall memory compared to recognition memory may be interpreted as indicating that stimuli that are sufficiently deeply encoded to be subsequently consciously recalled are subject to greater emotional modulation in patients than those that can be recognised later but not consciously recalled.

Previous studies of the modulatory effect of emotion on memory in schizophrenia have used word stimuli (Calev and Edelist, 1993; Danion et al., 2003; Koh et al., 1976; Mathews and Barch, 2004). Some of these studies have shown a relative preservation of emotional memory effects in schizophrenia in terms of both recall (Calev & Edelist 1993; Koh et al., 1976; Mathews and Barch 2004) and recognition (Mathews and Barch, 2004) whilst others have shown selective deficits in recognition memory (Danion et al., 2003). This inconsistent pattern of results may in part relate to the less emotionally arousing nature of word stimuli. Given the evidence that amygdala activation is only required to enhance memory for highly arousing stimuli many of these studies may have used cues that were of insufficient emotional intensity to demonstrate deficits in amygdala function. In contrast in the present study we have used pictorial stimuli from a well characterised battery that have been previously shown to both produce high subjective and autonomic arousal responses and to produce amygdala activation in functional neuroimaging studies (Canli et al., 2000; Hamann et al., 1999; Lang et al., 1997; Lang et al., 1993). In addition
some earlier studies have examined memory at short recall intervals (Danion et al., 2003; Koh et al., 1976; Mathews and Barch, 2004), although the effects of emotional arousal on memory consolidation are greatest after a delay (LaBar and Phelps, 1998). This is reflected in the finding of greater deficits in emotional memory in the delayed recall task in the present study.

Overall the present study showed both a selective impairment in emotional memory consistent with impaired amygdala function and a more general impairment in memory as a whole which is likely to derive from dysfunction of medial temporal lobe memory systems including the hippocampus. A particularly striking finding was the dissociation between intact subjective ratings of emotional arousal and impaired emotional enhancement of memory in subjects with schizophrenia, a finding that closely resembles that seen in individuals with selective amygdala damage (Adolphs et al. 1997; Cahill et al. 1995; Hamann et al. 1997).
4.5 Strengths and limitations

The major strength of the current study was the use of multiple neuropsychological approaches to test amygdala function in subjects with schizophrenia. This overcomes the limitations of previous work which has tended to focus only on tests of facial emotion recognition. Whilst deficits in facial emotion recognition have been demonstrated in a number of studies these could derive, at least in part, from impairments in other brain regions involved in faces processing. The present study provided more robust evidence of impaired amygdala function in schizophrenia by demonstrating that patients are impaired in a range of tasks dependent on this brain region.

The tasks used in this study have been directly drawn from those previously shown to be sensitive to lesions of the amygdala, and to produce activation of the amygdala in functional neuroimaging studies. This contrasts with previous investigations of emotional and social function in schizophrenia which have often used tasks for which the neural basis is uncertain. The present study represents the first investigation of social cognition from faces using tests shown to depend on amygdala function, and the first study of emotional memory in schizophrenia using emotional scenes known to activate the amygdala.

The limited sample size in the present study limits the strength of the conclusions that can be drawn from the results, in particular with regard to the relationship of the deficits to specific clinical states and symptoms. However as statistically robust deficits were demonstrated in all three main tasks the study was adequately powered for investigation of the performance of individuals with schizophrenia as a whole. Future replication of the present investigations is nevertheless required to substantiate these findings.
The patients in the current studies were all receiving antipsychotic medication and it is therefore possible that drug effects contributed to the deficits seen. However there were no correlations between dose of medication and performance on any of the measures of amygdala function in these studies. Furthermore acute administration of antipsychotic medication has not been found to impair facial emotion recognition (Harmer CJ personal communication) or emotional memory formation (Mehta et al., 2005). It is therefore unlikely that the deficits in emotional memory seen in the current study were due to treatment with antipsychotic medication, although this will only be confirmed by studies of medication free individuals.

Neuropsychological tests represent only an indirect measure of underlying brain function. Whilst the conclusions drawn from such tests regarding underlying neural function are enhanced by the use of multiple measures of the function of a particular brain region, more direct approaches are required to confirm the neural basis for the deficits seen. The tasks used in the current study were all designed to be transferable to the functional neuroimaging environment, permitting future direct investigation of the neural basis for the impairments in these tasks seen in patients with schizophrenia.
4.6 General conclusions

The studies conducted in this thesis set out to test the hypothesis that subjects with schizophrenia have deficits in a range of cognitive functions dependent on the amygdala. Overall patients showed significant deficits in all three neuropsychological tests of amygdala function conducted, providing convergent evidence for abnormal functioning of this brain region in individuals with schizophrenia.

These results however should not be taken to imply that schizophrenia is a disorder in which subjects effectively have a total lesion of the amygdala, or that the abnormalities in brain function in schizophrenia are restricted to this region. Amygdala volume in schizophrenia is only reduced by approximately 6-10% and pathological abnormalities are observed in a large number of brain regions in this disorder (Lawrie and Abukmeil, 1998; Wright et al., 2000). The consequences of such alterations in volume are yet to be fully established but the pathological processes may well lead to dysregulated, rather than absent, function of the amygdala.

Given the complex interactions of the amygdala with different brain regions in the tasks investigated it is not surprising that there was some variation in the pattern of deficits seen in the different tasks conducted. For example subjects showed impairments in facial emotion recognition only when experiencing positive symptoms, whereas social cognition was impaired across all subjects. In addition greater deficits were seen in the emotional enhancement of recognition memory than in the emotional modulation of recall memory. These differences are likely to reflect the different neural systems with which the amygdala interacts in these separate tests, as well as the degree to which impaired amygdala function can be compensated by other neural systems.
However, the demonstration of deficits in the performance of individuals with schizophrenia in a range of tasks, each of which involves the amygdala in the context of different neural circuits, provides particularly strong evidence for amygdala dysfunction in schizophrenia. For example, the emotional enhancement of memory depends upon an interaction between the amygdala and other medial temporal lobe memory systems, whilst social cognition depends upon the amygdala integrating with a separate group of brain areas including the medial prefrontal cortex and superior temporal gyrus. The finding of impairments in both these tasks strongly supports the view that amygdala function is impaired in schizophrenia.

The primary functions of the amygdala in emotional and social cognition relates strongly to the symptoms of schizophrenia. Abnormalities in emotional and social function are known to predate the onset of the full schizophrenia syndrome (Jones, 1997; Owens et al., 2005) and the acute presentation is most often associated with paranoid beliefs regarding the intentions of others and heightened arousal. Impairments in social function are a recognised concomitant of the disorder (APA, 1994). Furthermore progressive diminution of emotional reactivity accompanies the progression of the illness and the development of a deficit state. The present results suggest that amygdala dysfunction contributes to these impairments, although future work with larger numbers of subjects will be required to substantiate the relationship of abnormalities in amygdala function to different clinical states in schizophrenia.
4.7 Future research

The current studies suggest a number of directions for future research. Firstly, there have been very few studies of the performance of patients with schizophrenia on Pavlovian conditioning tasks known to depend upon the amygdala. Secondly, the role of abnormalities in amygdala function in the deficits seen in the tasks used in this thesis requires to be more directly investigated using functional neuroimaging, an approach that has only thus far been applied to tests of facial emotion recognition (Phillips et al., 1999; Gur et al., 2002). Thirdly, the present findings need to be substantiated in larger patient cohorts. The use of larger numbers of subjects would also allow more detailed investigation of the relationship of these behavioural deficits to different symptom states and to the overall course of the illness. Fourthly, it will be important to investigate the performance of unaffected relatives and high risk groups on the present tasks. There have been very few studies of the performance of relatives of patients with schizophrenia on emotion processing tasks but those that have been conducted suggest that abnormalities in emotion processing are also seen in unaffected first degree relatives, supporting the view that these deficits represent a heritable predisposition to the illness (Habel et al., 2004). Fifthly, it will be of interest to determine whether the functional abnormalities shown in individuals with schizophrenia in the current study are also seen in related functional psychoses such as bipolar disorder. Finally the identification of well replicated susceptibility genes for schizophrenia presents the possibility of investigating the genetic basis of deficits in emotional and social function in individuals with schizophrenia (Harrison and Weinberger, 2005).
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