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# Functional Disconnection and Social Cognition in Schizophrenia

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## Abstract

**Introduction** Social and emotional functions play a key role in schizophrenia. Both positive symptoms, such as hallucinations and persecutory delusions, as well as negative symptoms such as social withdrawal, and flattened affect impact socio-emotional function. These functions involve distributed brain networks. The 'Disconnection Hypothesis', a plausible unifying theory of schizophrenia, proposes connectivity within such networks as a core pathological feature of schizophrenia. Connectivity is also related to specific genetic risk factors. Therefore the present project addresses the hypothesis that individuals with schizophrenia might show disconnection within socio-emotional brain networks, and examines the effects of a functional polymorphism of the BDNF gene on connectivity within these networks.

**Methods** Here I examined the brain activation and connectivity for implicit emotional reaction and social judgment in schizophrenia, as well as with variation in the val66met polymorphism of BDNF. Brain activation was examined with functional magnetic resonance imaging, and effective connectivity was estimated using psycho-physiological interactions, from the bilateral amygdala to the whole brain (using a facial image paradigm for explicit approachability judgement and implicit fear response respectively).

**Results** Individuals with schizophrenia showed reduced activation in the right lingual gyrus, right superior temporal gyrus and left amygdala during fear processing, as well as reduced connectivity from the left amygdala to the right temporo-parietal junction and precuneus. During approachability judgments, patients overactivated the right inferior frontal gyrus and right precuneus and showed reduced connectivity from the bilateral amygdala to the right inferior frontal gyrus.

Met allele carriers of the BDNF val66met polymorphism showed overactivation in the medial anterior cingulate cortex, and bilateral insula, as well as reduced connectivity between the anterior cingulate cortex and hippocampus. For approachability judgment, met carriers overactivated the middle occipital gyrus, and showed reduced connectivity from the left amygdala to the right parahippocampal gyrus and medial frontal gyrus, as well as the left posterior cingulate gyrus, pre and post central gyrus, middle temporal gyrus and cerebellum.

**Conclusion** In conclusion, connectivity between the amygdala and brain regions associated with a range of socially relevant functions were found to be reduced in both patients, and met allele carriers of the BDNF val66met SNP. Given the key role of the amygdala in affective processing this diffuse disconnection in networks for socio-emotional functions might mediate the aberrant emotional and social behavior seen in individuals with schizophrenia.

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# Declaration

I declare that this thesis was composed by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification except as specified.

Prerona Mukherjee

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# CHAPTER ONE:

# INTRODUCTION

## 1.1 Schizophrenia: A Brief Introduction

### 1.1.1 Defining Schizophrenia

*"The spirit that I have seen*

*May be the devil: and the devil hath power*

*To assume a pleasing shape; yea, and perhaps*

*Out of my weakness and my melancholy,*

*As he is very potent with such spirits,*

*Abuses me to damn me."*

The quote above is from William Shakespeare's play Hamlet (Act II, Scene 2). In this play, Hamlet, the prince of Denmark, sinks in melancholy after his father's death. He experiences harrowing visions, which he attributes to his fathers spirit. He believes his mother and uncle are conspiring to persecute him. He claims to find himself gripped by wild and whirling emotions, as well as mood shifts from deep depression to wild elation. He breaks with his lover because he feels unable to care for her, and retreats from his affairs of business out of apathy and preoccupation with his otiose melancholy. Hamlet's condition features some of the common symptoms of schizophrenia. Nevertheless, at the time of Shakespear's writing the play, Hamlet's condition might have been diagnosed as 'melancholy adust', as defined in 'A Treatise of Melancholy' by Timothy Bright (1586) and 'The Anatomy of Melancholy' by Robert Burton (1621). In hindsight, it is difficult to be sure if Hamlet did suffer from schizophrenia, in large part due to one of the main challenges of the disorder: schizophrenia is extremely difficult to define.

It is uncertain when schizophrenia first came into existence (Jeste et al., 1985, Hare, 1988), although the syndrome was not clearly described until Kraepelin defined dementia praecox as a disorder similar to dementia in young individuals (Emil Kraepelin in 1899). This was later redefined by Bleuler, who was the first to use the word schizophrenia, derived from the Greek term for 'split brain'. Schizophrenia is a severely debilitating disorder which impacts about one percent of the world population (Murray and Lopez, 1997). Yet, it's precise characterisation remains disputed. Indeed, schizophrenia has been called the 'most mysterious' of brain disorders (van Os and Kapur, 2009). Despite many theories, there is no unified consensus regarding the aetiology of schizophrenia or the underlying morbid process. Therefore it remains characterised on a clinical basis (DSM-IV).

### 1.1.2 Symptoms of Schizophrenia

Schizophrenia impacts the most high level human brain functions. It is not characterised by any one particular symptom, but patients suffer from a variety of positive and negative symptoms (Crow, 1980). Positive symptoms including behavioural excesses such as auditory and visual hallucinations, delusional ideation, and thought disorder take patients away from reality. Negative symptoms, or behavioural deficits, such as social withdrawal, lack of motivation, flattened affect, a loss of ability to feel pleasure (anhedonia) and poverty of speech (alogia) affect interactions with others.

### 1.1.3 The Social Cost of Schizophrenia

Schizophrenia impacts about one percent of the world population (Murray and Lopez, 1997), or about 60 million people worldwide (Knapp, 1997, Knapp, 2004, Knapp, 2005). Most of these cases lead to a loss of normal functioning and some eventually progress to severe impairment or suicide (Hor and Taylor, 2010, Hawton et al., 2005, Ajdacic-Gross et al., 2007). Not just the patient, but the family, and society as a whole is affected (Awad and Voruganti, 2008, Caqueo-Urizar et al., 2009, Mitsonis et al., 2010, Reine et al., 2003).

As patients need care and monitoring, this imposes a tremendous financial burden on society (Wasylenki 1994, Knapp and Kavanagh 1997, Heider, et al., 2009). Some patients have children who consequently often face highly disrupted family lives requiring appropriate intervention programs (Craig and Bromet, 2004). In 2005, the total cost to society due to this illness was estimated at 6.7 billion pounds in England (Mangalore and Knapp, 2007). In the UK in 1992–93, direct costs of caring for people with schizophrenia were £810 million, accounting for 2.76 per cent of the total health expenditure by the National Health Service, and inpatient care for individuals with schizophrenia cost 5.37 per cent of the total hospital costs (Knapp, 1997). These factors have excited a massive amount of research on the disorder in recent times.

### 1.1.4 Existing Theories and Research on Schizophrenia

Several theories have been proposed regarding the causes and basis of schizophrenia. Nevertheless, there is no clear consensus on any one that conclusively explains all of

the features of the disorder. In general terms, a physiological basis is believed to interact with environmental factors (Zubin and Spring 1977). Diverse factors including season of birth and socio-economic status have been associated with schizophrenia, with no conclusive evidence. It is, however, generally agreed that genetic, environmental, neurological and neurotransmitter dysfunction play an interacting role (Picchioni and Murray, 2007, Os and Kapur, 2009).

It has also been suggested that such mental phenomenon are reasonable results of the pressures of modern society, or "a perfectly rational adjustment to an insane world" (Laing, 1964). He proposes that complex and contrasting social messages can confuse and overwhelm brain development, leading to breakdown, and points out that schizophrenia is characterised by behaviour but treated biologically. Laing suggests behavior and speech of patients were understandable attempts to communicate extreme internal experiences. To quote again from Shakespeare, two of Hamlets friends debating on how to interpret his behaviour argue "He talks to himself which you'd think was madness except that he makes sense when he does it. And the way I see it is that a man talking sense to himself is no madder than a man talking nonsense not to himself. Or just as mad. He does both. So there you have it. Stark raving sane". Indeed, schizophrenia has also been called an evolutionary cost to increased human mental capacities such as language (Crow, 1997).

Some prominent theories proposed towards modelling schizophrenia include the dopamine theory (Carlsson and Lindqvist, 1963), neuro-developmental theory (Weinberger, 1987), glutamate theory (Olney & Farber, 1995), a number of cognitive models including executive function theory, attentional bias, latent inhibition (Lubow and Gewirtz, 1995, Broome et al., 2005, Beck 2004), the stress-vulnerability model

(Zubin and Spring, 1977), the 'Disconnection Hypothesis' (Friston, 1998) and the 'Social Cognition Theory' of schizophrenia (Burns, 2004).

I have chosen to focus on social cognition disruptions in schizophrenia in terms of the disconnection hypothesis (Friston, 1998), together with genetic factors associated with schizophrenia (Harrison and Owen, 2003), which could impact upon this 'connection' (Stephan et al., 2006). These concepts are discussed in depth in the following sections.

## 1.2 Emotional Function in Schizophrenia

### 1.2.1 About Emotions

Science has from the earliest times tried to separate reason and emotion, despite Hume's assertion that "reason is, and ought only to be, the slave of the passions" (Hume, 1739). Traditionally emotions have been associated with neurosis, mania, irrational behaviour, as opposed to reason and dispassionate control. A yin-yan, negative-positive approach to emotion versus cognition has been traditionally popular (Damasio, 1996). It has been recently reiterated, however, that emotions are vital for efficient function and work together in concert with cognitive systems (LeDoux, 1996).

The role played by emotions has been explained in several ways. Emotions have been associated with somatic markers or labels which help categorise information (Damasio, 1996), as well as signals providing instantaneous information, or perception of bodily states (James, 1884, Lange 1885). Aligned with an individual's internal goals and motivations, emotions form an instantaneous relation to the environmental of the individual (Rolls et al., 1998, Damasio, 1996, LeDoux 1996, Berridge 2003).

It has been suggested that understanding the function of a particular emotion, such as fear, might eventually elucidate the role of emotions in general (LeDoux 1996). In the present project, I have focussed on the emotion of fear. Although fear is a very basic and common human emotion, it is traditionally considered as a negative, as something that holds individuals back from action. Nevertheless, it can also be

seen as one of the most crucial aspects of the human survival mechanism. In this way we can interpret fear as a signal which enhances an individual's probability of survival by raising an alarm when a threat is detected.

This alarm system has been extensively studied and shown to be nearly instantaneous, in many cases being set in motion before the individual is even consciously aware of the threat, therefore enabling the most rapid reaction in self-defense (Liddell 2004, Davis and Whalen, 2001, Ochsner et al., 2008). To maximise survival it makes sense that this alarm would be triggered at any suspicion of threat, even before the individual can cognitive appraise the situation, and can be modulated by slower cognitive processes subsequently if necessary. This cognitive appraisal might involve processing the entire environmental context related to the 'threat input', information, and past experiences in memory (Sotres-Bayon and Quirk, 2010). Therefore as a system the cognitive and emotional processes interact to determine the ultimate behaviour of the individual (Nili et al., 2010, Ochsner and Gross, 2005, Delgado et al., 2008, Ahs et al., 2009, LeDoux, 1996). This interaction is thus vital to obtain the balance between safety and reasonable behaviour. On seeing an image of a dangerous predator, a subject might, for example, feel an instinctive emotion of fear. On further thought, and evaluation of the difference between a real predator and an image, the subject might consciously suppress this feeling. However if this regulatory interaction between the emotional and cognitive is disrupted or distorted, the emotion of fear might not be regulated appropriately, as the larger context demands (Sotres-Bayon and Quirk, 2010).

Facial expressions are one of the chief ways in which emotion is conveyed between individuals. It has been suggested that due to the key role faces, special

brain systems exist for facial processing, as discussed in detail below. Further, evaluating emotion from another individuals face has shown to evoke similar brain responses as first hand emotion, due to 'Emotional Contagion' (Singer et al., 2004b). In the case of fear, this would evolutionarily allow alarm of threat in the same geographic vicinity to spread effectively (Gelder et al., 2004). This implies the brain response to viewing expressions of fear on another individual would be similar to the brain response to first hand experience of fear. In the present study I have used this as a basis to investigate brain response to implicit fear processing by showing subjects faces expressing a fearful expression.

### 1.2.2 Neural Basis of Emotional Function

The neural basis of emotion processing, particularly from faces, has been studied extensively as discussed briefly in this section (for extensive review see Fusar-Poli et al., 2009, Murphy et al., 2003, Adolphs 2002, Kober et al., 2008). It has been shown repeatedly that there is a subcortical face processing network which can instantaneously analyse emotional information from faces, even before conscious perception (Johnson, 2005, Johnson et al., 2005, Liddell 2004).

The amygdala is the region most strongly associated with fear processing (Adolphs et al., 1998, Allman and Brothers, 1994), as discussed in detail in section 1.7. Other limbic regions such as basal ganglia, temporal polar cortex, perirhinal cortex and insula, as well as visual regions such as inferior occipital gyrus, fusiform gyrus, and superior temporal gyrus, and cognitive regions such as the ventromedial, ventrolateral and the medial prefrontal cortex, inferior frontal gyrus, anterior cingulate cortex, orbitofrontal cortex are believed to be involved, as well as parts of

the occipital gyrus, occipitotemporal cortices, parahippocampal gyrus, parieto-occipital cortex (Haxby et al., 2002, Phillips et al., 2003a,b, Adolphs 2002). The functions of these regions are discussed in greater detail in following sections.

Different parts of this network have been suggested to be involved in separate aspects of emotion processing (Kober et al., 2008), and different emotions (Calder et al., 2001). The parahippocampal structures are believed to play a prominent role in evaluating context for storage and retrieval (Kilpatrick and Cahill, 2003). The insula has been shown to be involved in processing empathy (Singer et al, 2004b), and the ventral striatum associated with motivation. The orbitofrontal cortex (Rolls et al., 1999), anterior cingulate cortex (Allman et al., 2001) and other frontal regions including the medial prefrontal cortex (Sprengelmeyer et al., 1998, Damasio et al., 1990, Sotres-Bayon and Quirk, 2010) are suggested to regulate the expression and extinction of emotion, having access to more contextual information. The cerebellum has also been associated with in social function (Schmahmann and Sherman 1998, Schmahmann 2004). The temporo-parietal cortex is believed to play a key role in theory of mind, or thinking about other people's intentions (Brass et al., 2005, Perner et al., 2006, Saxe, 2006, Saxe and Kanwisher, 2003, Young and Saxe, 2008, 2009a, b, Benedetti et al., 2009). Additionally, the precuneus also is associated with mentalizing and theory of mind (Mar, 2011), as well as self related processing, or taking a first person perspective (Cavanna and Trimble, 2006). Some of these regions are reviewed in Mandal et al., 1996.

Due to the widely distributed nature, connectivity between different parts, especially fronto-temporal interactions, is critical to function. Figure 1.2.1 below (from Kober et al., 2008) shows some of the cortical and sub-cortical regions found

to be involved in emotion processing in a meta-analysis, and the interactions between them. Interactions such as these constitute the connectivity investigated in the present study. Some of the important connections are discussed in the following sections.

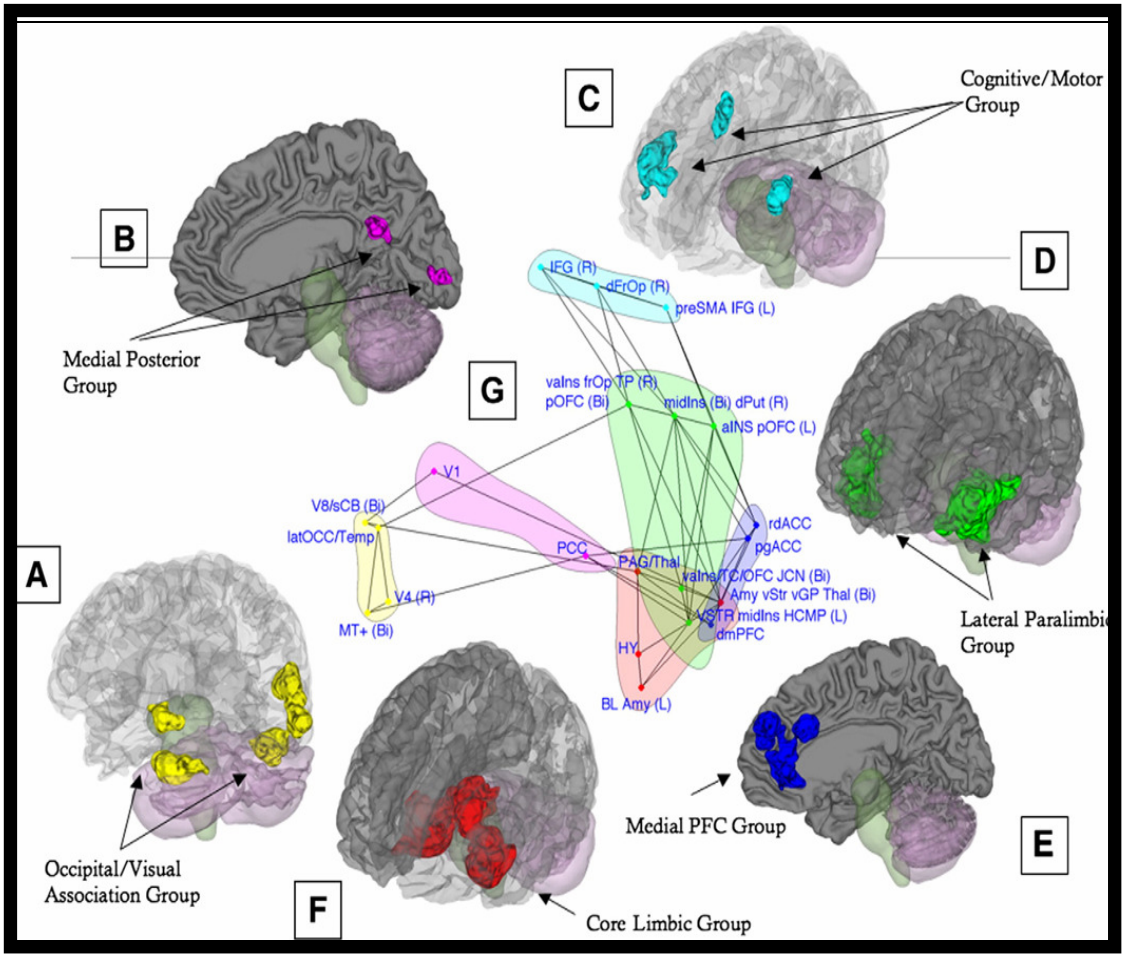



**Figure 1.2.1: Cortical and subcortical brain regions involved in emotion processing.** (A–F): The six functional groups revealed by multivariate analysis are depicted in 3D rendering on the single-subject brain. From Kober et al., 2008.

### 1.2.3 Fronto-Temporal Interactions in Emotional Processing

Emotion appears to be processed in a two pass feed-forward / feed-back model combining both top-down and bottom-up processing (Ochsner et al., 2009, Scherer, Schorr and Johnstone 2001, LeDoux 1996, Aggleton 1993, Davis and Whalen, 2001, Amaral et al., 2003, Amaral and Price, 1984). Certain classes of information, such a gender and basic emotion, is instantaneously gleaned. More nuanced information might then be processed by slower parts of the system, as shown in figure 1.2.2 below (Adolphs 2002, Nili et al., 2010, Ochsner and Gross, 2005). Several regions, including the amygdala and other temporal regions, along with the anterior cingulate cortex and orbitofrontal cortex are believed to be involved. Therefore, interactions between different parts of this distributed network, particularly frontal-temporal interactions between cognitive and emotional regions play a vital role (Delgado et al., 2008, Ahs et al., 2009, LeDoux 1996, Aggleton 1993, Davis and Whalen, 2001, Amaral et al., 2003, Amaral and Price, 1984, Vuilleumier et al., 2004, Vuilleumier and Pourtois, 2006). Interactions between the medial prefrontal and orbitofrontal regions with amygdala have been shown to be crucial to fear extinction, inhibition and expression in animal (Sotres-Bayon and Quirk, 2010) and imaging studies (Murray and Wise 2010). Therefore disrupted connectivity between these brain regions, such as the disconnection investigated in the present study, might significantly affect these interactions, and thereby emotional function.

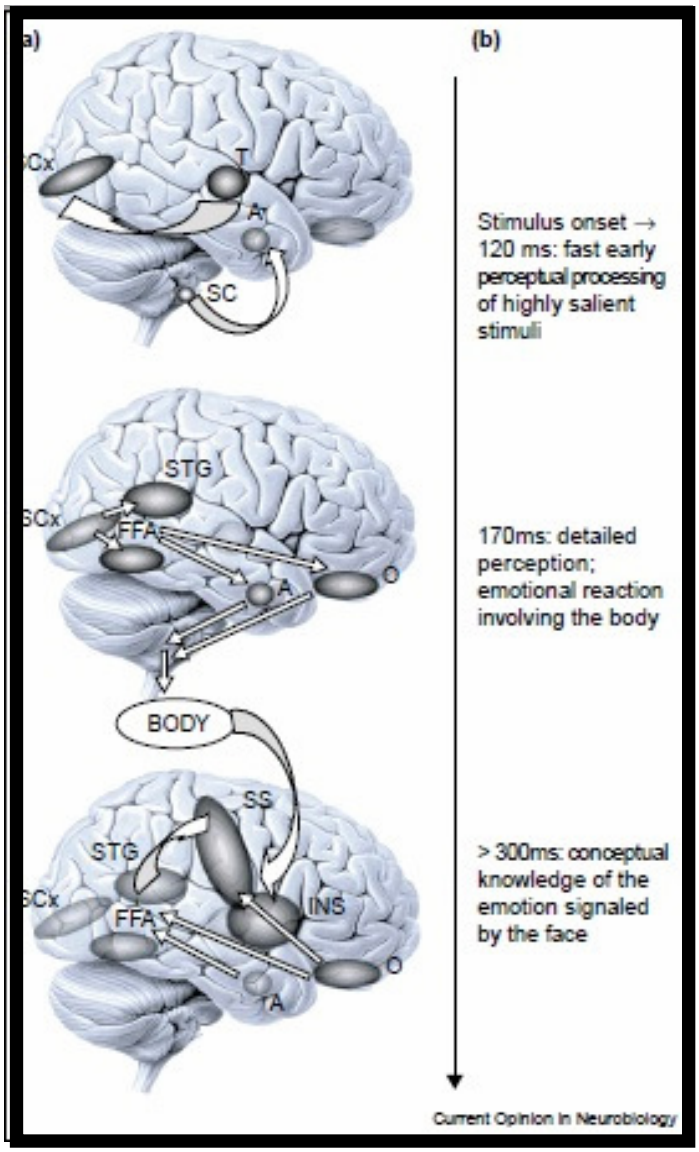



**Figure 1.2.2: Processing of emotional facial expressions as a function of time.**
Structures involved in emotion recognition at various time points. A, amygdala; FFA, fusiform face area; INS, insula; O, orbitofrontal cortex; SC, superior colliculus; SCx, striate cortex; SS, somatosensory cortex; STG, superior temporal gyrus; T, thalamus. From Adolphs 2002.

### 1.2.4 Emotional Disturbances in Schizophrenia

Several aspects of emotional function have been shown to be impacted in Schizophrenia, particularly related to facial emotion (Mandal et al., 1998, Edwards et al., 2001, Edwards et al., 2002, Pinkham et al., 2003, Dougherty et al., 1974). These include expression, experience (Baslet et al., 2009) and recognition (Trémeau, 2006, Marwick and Hall 2008, Kohler et al., 2010). This is particularly true for negative emotions including fear (Benedetti et al., 2011, Henry et al., 2007, Cutting 2006, Edwards et al., 2001).

Many of the symptoms of schizophrenia, such as paranoia, persecutory delusions, are related to emotional disturbances, particularly as related to the emotion of fear or threat. Imaging studies have indicated fear processing deficits to be correlated with symptoms (Michalopoulou et al., 2008, An, et al., 2006). This effect has also been shown in terms of autonomic arousal or skin conductance (Williams et al., 2007).

Several functional abnormalities have been shown in schizophrenia for brain regions associated with fear processing. These regions include the amygdala (Namiki et al., 2007, Kosaka, 2002, Gur, 2007, Holt et al., 2006, Hall et al., 2008, Kohler et al., 2010), parahippocampal gyrus (Surguladze et al., 2006), orbitofrontal cortex, medial prefrontal cortex, superior frontal gyrus, fusiform gyrus, middle occipital gyrus (Li et al., 2010, Suzuki et al., 2005). Further, the connections in the fear processing brain network have been shown as impacted in structural (Good 2001) and functional connectivity studies (Benes 2010, Das et al., 2007). Fronto-temporal dysregulation in particular has been shown for processing angry faces (Radulescu

and Mujica-Parodi, 2008). Such an effect on emotion processing might be of prime importance in social behaviour, and highlights the importance of emotion processing in a social context.

## 1.3 Social Cognition and Schizophrenia

### 1.3.1 Social Cognition

Navigating a complex social environment has evolutionarily been crucial to human survival, and social cognition refers to all related brain functions. Social cognition is suggested as having subsidiary components including emotion processing, theory of mind, and social judgement (Lieberman, 2007). Therefore, some of the concepts discussed in this section have also been mentioned earlier in section 1.2.1 on emotion processing. The brain processes related to social function include representation of internal states, processing somatic markers, knowledge about self, perceiving others as individuals and processing the mental states, beliefs and motivations of other individuals, and interpersonal interactions (Amodio and Frith, 2006).

A key social skill is making judgements regarding another individual from their face. These judgements include facial identity, facial expression, gaze direction, body language, and information about social context (Adolphs, 2001, Hall, 2004, Brothers, 1990). Due to the importance of facially coded information, it has been suggested that specific brain systems might exist for this (Adolphs, 2003a). Faces could encode categorical information regarding the individual, such as identity, gender, age, or basic emotions such as fear, anger, happiness, surprise as well as more subtle judgment of social valence, such as attractiveness, usefulness, social position, approachability, intelligence. Facial processing has been categorized variously as processing identity and facial expressions of emotion (Bruce and Young, 1986), or variant and invariant aspects (Haxby et al., 2000).

Emotional information is an important feature of social function and processing emotional expressions is complex, therefore much of the specialized brain circuitry for facial processing is likely to be for this aspect (Haxby et al., 2000, Calder and Young, 2005). The neural basis of facial processing has been studied extensively, in health (discussed in the following section), as well as in disorders such as schizophrenia (as discussed in section 1.3.3).

### 1.3.2 Neural Basis of Social Cognition

The brain regions associated with social cognition, in general, and face processing in particular has been extensively studied. Some of these are discussed earlier in section 1.2.2. Making such socially relevant decisions from faces is subserved by a distributed network of brain regions, also known as 'The Social Brain' (Adolphs 2001).

The amygdala is a major hub in this network (Benes 2010), playing a key role in evaluating the emotional salience of social stimuli (Bickart et al., 2010, Vuilleumier & Pourtois, 2007, Adolphs, 2003b, Baron-Cohen, 2003, Brothers, 1990). This is discussed in detail in section 1.7. Other regions such as the orbitofrontal cortex (OFC), anterior and posterior cingulate cortex, dorsolateral prefrontal cortex and medial prefrontal cortex (MPFC), left parietal cortex, and the amygdala, have been suggested to be involved in social cognition (Brothers, 1990, Adolphs, 2001, Adolphs, 2003, Amadio and Frith, 2006). The prefrontal cortex is associated with acquiring, representing and retrieving the expected value of actions and anticipating future outcomes of decisions, as indicated by various animal, lesion, imaging, single cell and grey matter volume studies. The fusiform gyrus (FG), also known as the face

area, is believed to play a central role in the invariant aspects of facial processing, such as feature recognition and identity determination (Kanwisher et al., 1997). The superior temporal sulcus (STS) and lingual gyrus are also believed to be involved in processing expression and gaze (Brothers, 1990, Adolphs, 2001, Haxby et al., 2000, Kemotsu, et al., 2005, Allison et al., 2000). The right somatosensory cortices, including the SI, SII, insula and the anterior supramarginal gyrus, have been shown to be involved in evaluating the emotional state of another individual from their facial expression (Adolphs, 2001). The prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) are associated with emotion, attention and executive functioning, influencing the response to stimulus, decisions, and volitional control of behaviour. Damage to both the amygdala and the frontal cortex have also been associated with theory of mind and empathy, indicating an association with reasoning about mental states of others (Lee at al, 2004, Stone et al., 1998, Stuss et al., 2001, Adolphs, Tranel and Damasio, 1998, Fine et al., 2001).

Single cell studies show large, spindle shaped neurons found exclusively in the ACC of primates, their density being highest in humans. Although the exact function of these cells is not known, their axonal length indicates that they might be involved in connecting these brain regions with distant brain regions. It is possible that they might enable the integration of different modalities of information in the ACC. Studies of patients undergoing neurosurgery also associate this region with a mirror neuron system including response to perceived pain (Adolphs, 2001). Together this evidence supports a cognitive regulatory role of the ACC in socio-emotional behaviour, particularly in humans.

The OFC is associated with social behaviour in both primates and humans. In humans, it corresponds to future planning, response to punishment, social manners and concern for other individuals as shown by lesion studies. In addition, both animal and human studies link it to processing of emotionally or socially aversive stimulus (Adolphs, 2001). The OFC has also been associated with processing facial expression, especially judging attractiveness of perceived faces (O'Doherty et al., 2003, Winston et al., 2007).

The ventral PFC is suggested to be involved in linking interoceptive and exteroceptive information, together with the amygdala and ventral striatum, while the ventromedial prefrontal cortex is associated with making 'gut feeling' based choices (Damasio, 1994, Adolphs, 2001). The MPFC has been associated with theory of mind as well as self-control and other executive functions (Fletcher at al, 1995a, Happe et al., 1996, Gallagher et al., 2000, Adolphs, 2001) and social judgement (Amadio and Frith, 2006). Further, the inferior frontal gyrus (IFG) has also been associated with various aspects of social judgement, including the mirror neuron system, empathy as well as assessing risk to oneself (Keuken et al., 2011, Ramsey and Hamilton, 2010, Knoch et al., 2006). The DLPFC has also been associated with theory of mind in imaging studies (Russell et al., 2000, Amadio and Frith, 2006). The cerebellum has also been shown in recent lesion and psychological studies to be involved in higher and executive functions (Schmahmann, 2004, Schmahmann & Sherman, 1998).

Interaction between these distributed brain regions, particularly fronto-temporal interactions between cognitive and affective regions, is critical, as discussed in section 1.2.3. Prefrontal and temporal parts of this distributed network

are believed to be important, due to their suggested roles in cognitive and affective aspects of brain function respectively, both of which are critical for effective social function (Adolphs, 2001, Winston et al., 2003).

### 1.3.3 Disrupted Social Cognition in Schizophrenia

Many of the affected cognitive functions in schizophrenia fall within the domain of social cognition. Social Cognition, as defined above, has been demonstrated to be impaired in several studies of schizophrenia (Hall et al 2004, Nordt et al., 2007, Green et al., 2007). In many cases patients have been found to have abnormal functioning related to social cognition, and especially in its threat related aspects (Phillips et al., 2000, Baron-Cohen et al., 1999).

Deficits in facial information processing, especially related to processing emotion or affect has been demonstrated in schizophrenia (Addington and Addington, 1998, Martin et al., 2005, Gur et al., 2002). Schizophrenia is characterized by behavioral deficits in social cognition, and making social judgments from faces in particular (Mandal et al., 1998, Cutting, 2006, Edwards et al., 2001, Edwards et al., 2002). The social brain hypothesis suggests, that dysfunction within the social brain, or the distributed network which subserves social cognition, is a key aetiological factor in schizophrenia (Burns 2006). Earlier studies demonstrated that patients exhibit behavioral deficits in social cognition, particularly in face processing, and these were suggested to be caused by functional disconnectivity between frontal and temporal brain regions (Hall et al., 2004). Moreover, disrupted social cognition could be related to several symptoms of schizophrenia. A related theory proposed by Frith (Frith, 1992) is based on a deficit in the 'Theory of Mind'

capacity, introduced by Premack and Woodruff in 1978, which refers to a person's ability to have a theory about or reason about the state of mind of another person.

Many of the brain regions involved in social cognition, and in theory of mind are also found to be impacted in post-mortem and imaging studies of individuals with schizophrenia (Lee et al., 2004, Burns, 2004). Many of these theories about schizophrenia, as well as many of the chief symptoms of the disorder, imply that deficits in social behaviour are of key importance in schizophrenia. Several of the brain regions underlying social cognition, as discussed in the previous section, have also been reported as impaired in schizophrenia, both structurally and functionally. Structural studies indicate that regions including the amygdala and prefrontal and superior temporal cortex are seen to be reduced in volume in Schizophrenia patients (Wright et al., 2000). Previous functional imaging studies have shown that, although the brain activations were similar between groups for fearful stimuli, patients with schizophrenia showed a relative overactivation of the amygdala for the neutral stimuli compared to control subjects (Hall et al., 2008, Holt et al., 2006 , Seiferth 2008).

Several studies have found behavioural deficits in social cognition in schizophrenia. These consist of inaccurate evaluations of social input (Ozenoglu et al., 2007, Ajdacic-Gross et al., 2007, Hall et al., 2004, Nordt et al., 2007, Green et al., 2007, Phillips et al., 2000, Burns, 2004, Eack et al., 2008), and faulty affect processing, including paranoia, where patients inaccurately process neutral stimulus as threatening (Phillips et al., 2000, Baron-Cohen et al., 1999). These behavioural deficits might cause faulty theory of mind and empathy processing, leading to inaccuracy in maintaining and processing information about the mental states, beliefs

and intentions of another individual (Frith, 1992, Broks, 1997, Lee et al., 2004). Further, innocuous stimuli may be aberrantly processed as threatening. Behavioural studies have also found deficits in recognition of negative affect, especially fear, from facial images in schizophrenia (Michalopoulou, 2008, Mandal et al., 1998). Imaging studies of trustworthiness judgments (Baas et al., 2008a), empathy (Lee et al., 2004) and theory of mind (Russell et al., 2000) have found increased overall amygdala activation in patients and reduced activation in the PFC and OFC.

To summarise, social cognition is generally impacted in schizophrenia, as evidenced both by behavioural studies, brain imaging studies, resulting in abnormal social behaviour, which might be related to several symptoms of the disorder (Phillips 2003a,b). Additionally, many of the brain regions in the social cognition network, and white matter tracts between them (Burns et al., 2003, Frith et al., 1995, McGuire and Frith, 1996), are also implicated in schizophrenia.

These brain regions in the social cognition network which act in concert, or are 'functionally connected', in the same way as described earlier for emotional function. Given that the disconnection hypothesis suggests that disconnectivity between brain regions is a core pathological feature of schizophrenia (Friston, 1998, McGuire and Frith, 1996, Stephan et al., 2009), such disconnection within these networks might mediate abnormal social and emotional behaviour associated with schizophrenia.

## 1.4 Functional Segregation and Integration in the Brain

Two main concepts have been employed in understanding brain function. These are functional segregation, which posits that individual brain regions might be specialized in performing distinct brain functions, and functional integration, which suggests integration between brain systems might underlie distinct brain functions. The following two sections discuss functional segregation and integration, and define the related terms including connectivity, as referred to in the rest of this study.

### 1.4.1 Functional Segregation and Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (fMRI) is a brain imaging method allowing non-invasive in-vivo investigation of neural activity during experimentally manipulated psychological context. fMRI measures the magnetic resonance properties of haemoglobin in blood, which varies with the blood oxygenation level, providing an indirect measure of the level of oxygen in the blood. Based on the principle that increased activity in a brain region will result in increased flow of oxygenated blood, this measure provides an indirect estimate of neural activity across different parts of the brain. The principles governing blood flow and oxygenation are called haemodynamics. As neurons do not have direct energy sources but only get supplied energy from blood, more active neurons will need to be supplied with energy by the blood at a higher rate. This Blood Oxygen Level Dependant (BOLD) contrast, allows researchers to determine which parts of the brain are likely to be more active (Yablonskiy, Haacke 1994). The observed fMRI signal is convolved with the BOLD function, which is based on observable

haemodynamics and sometimes called the haemodynamic response function. Brain activity is estimated while a subject is either at rest or performing an experimental task. Measuring the difference in activations for the experimental condition and at rest indicates brain regions involved in the task. Functional imaging studies have recently become more sophisticated and their applications in psychology have increased. Scanners have become faster, and new methods have improved the image resolution and contrast (Cage et al., 2007).

Two principles of brain function are applied to such data. These are functional specialization and functional integration. Functional specialization, described above, is based on the idea of individual brain regions specializing in specific psychological functions. Functional integration is based on the idea that spatially distant brain regions work in concert to perform specific psychological functions. Advanced statistical models are used on regional activation data, derived as described above, to calculate correlations in activation between different brain regions, or connectivity, as described in detail in the following sections (Friston 1997, Lee et al., 2003).

### 1.4.2 Functional Integration and Connectivity

Functional connectivity describes "temporal correlations between spatially remote neuro-physiological events" (Friston et al., 1993). This kind of interaction was referred to earlier using data such as EEG (Gerstein and Perkel 1969, Gochin et al., 1991, Aertsen and Preissl 1991). Functional connectivity referred to here is derived from functional imaging data, based on correlation between activation in brain regions, and is an estimate of functional integration between spatially separate

regions (Friston et al., 1993, Friston, 1994, Lee et al., 2003, Rogers et al., 2007, Horwitz, 2003). Such connectivity specifies the degree to which two brain regions are co-activated at the same time, and may or may not be mediated by direct anatomic connections (Friston et al., 1993, Friston, 1994, Lee et al., 2003, Rykhlevskaia et al., 2008). Functional connectivity is mediated by factors including synaptic plasticity and neuro-transmitter activity and cellular morphology and cytoarchitectonics (Friston et al., 2003, Zhang and Poo 2001, Stephan et al., 2006). Effective connectivity, defined as 'the influence that one neural system exerts over another (Friston et al., 1994), extends this by inferring the directionality that one of these connected regions is driving the activity in the other region of this connection (Friston et al., 1993, Horwitz, 2003).

It is believed that both principles of functional segregation and integration are present in the brain (Whalley et al., 2009). That is there are some individual units which perform specialized functions, such as motor and affective functions. These combine to form complex networks performing higher level functions. Each elementary unit could, however, participate in multiple high level composite networks, performing dynamic and context sensitive roles in each (Friston, 2002). These interactions between elementary functional units involve both driving or feed-forward, and modulatory or feed-back connections (Pessoa, 2008). In the present study the term connectivity results refer to effective connectivity.

### 1.4.3 Limitations of fMRI and Connectivity

Although fMRI provides an in-vivo method of estimating neural activity across the brain in an experimentally manipulated psychological context, there are a few

limitations of this technique. Firstly there is a high degree of noise in the data collected. The spatial resolution is relatively low (tens of thousands of neurons per voxel). It is relatively slow (seconds) compared with neuronal events (tens of milli-seconds). It is an indirect measure of neuronal activity, indexed by blood flow and metabolism, and the connection between these factors is not completely understood (Horwitz, 2003, Fingelkurts et al., 2005, Kim et al., 2006, Kim et al, 2000, Kim and Horwitz, 2008). In certain brain regions there are susceptibility artefacts, due to a variety of factors. Finally connectivity does not distinguish between inhibitory versus excitatory neurotransmission and cannot be directly related to anatomic connections (Moonen & Bandettini, 2000, Whalley et al., 2009). In spite of these limitations, however, imaging approaches to connectivity in vivo have gained popularity and a vast number of studies have demonstrated feasible results, which agree with earlier understanding of brain function based on other methods including PET and SPECT (Whalley et al., 2009, Frackowiak et al., 2002). The implications and limitations of connectivity have been elaborated further in the general discussion (Chapter seven).

### 1.4.4 Methods used to Estimate Connectivity

Several methods have been developed for estimating connectivity using various metrics to assess different temporal characteristics of the imaging time series (Whalley et al., 2009, Rogers et al., 2007). These methods may be divided into data-driven methods, which scan the whole brain for connected regions and model-driven methods, where an apriori model derived from prior anatomical knowledge is measured (Rogers et al., 2007). The first method has the advantage of discovering unanticipated connections, the second avoids the pitfall of over-fitting the data,

making it the more robust of the two, but at the risk of a poor fit between model and data. Some of the more common methods used are described below. Other methods exist, including dynamic causal modelling (Friston et al., 2003), Bayesian inference (Patel et al., 2006) and independent components analysis (Kiviniemi et al., 2003, Van de Ven et al., 2004, Beckmann et al., 2005). The method used in the present study is PPI. This method has been conceptually introduced below, while specific implementation details are discussed in Chapter two, and further implications and limitations of the method, as well as a comparison with other methods elaborated further in the general discussion (Chapter seven).

#### 1.4.4.1 Seed voxel correlation maps, or Pearson correlational technique:

This method has been widely used (Deary et al., 2004, Whalley et al., 2005, Rowe et al., 2002a, Rowe et al., 2002b, Rogers et al., 2004, Rowe et al., 2005, Lowe 1998, Hampson et al., 2002). Here functional connectivity between two brain regions is estimated by computing the Pearson correlation coefficient of their extracted time course. This might be confounded by common noise. Thus, anticipated confounds are added to a model, and the residual in the time-series data, after filtering it with this model, is used for calculating correlations (Whalley et al., 2009).

#### 1.4.4.2 Principal components analysis (PCA):

PCA takes a set of correlated variables and groups them into uncorrelated components, to account for variability in the data. The first component accounts for the maximum variability and subsequent components account for successively less. For each component, an eigenimage represents the spatial distribution of the variation, and an associated eigenvector can represent the temporal, or between subject variation (Andersen et al., 1999). PCA is used for data-driven analysis. This

method has been widely applied for imaging studies, usually across the whole brain, and many variations exist (Friston et al., 1993, Bullmore et al., 1996, Marshall et al., 2004, Sugiura et al., 2004). When applied to fMRI data a high number of eigenimage / time course pairs may be produced so careful correction for multiple testing is required. Furthermore, a single feature of interest tends get distributed across more than one component, which can make interpretation of results difficult (Rogers et al., 2007, Andersen et al., 1999).

#### 1.4.4.3 Partial least squares (PLS):

PLS is similar to PCA, but instead the data's covariance with a variable of interest is calculated. This variable could consist of the difference between experimental conditions or selected behavioural/clinical measures (Rogers et al., 2007). The method results in estimates of latent variables and score vectors. It is mostly used for whole brain analysis but can also be used for inter-regional analyses. Latent variables represent brain regions with their activity being represented by score vectors (Rogers et al., 2007). The method was first used in PET studies (McIntosh and Gonzalez-Lima, 1993, Nyberg et al., 2000, McIntosh et al., 1999, McIntosh et al., 2003, Kilpatrick et al., 2006) and a spatio-temporal variant was developed for fMRI analysis (McIntosh, et al., 2004, McIntosh et al., 1997, Addis et al., 2004, Caplan et al., 2006).

#### 1.4.4.4 Autoregressive models:

Autoregressive models estimate effective connectivity by incorporating temporal information from the signal into the calculation, along with the spatial aspect (Harrison et al., 2003). This method is based on the fact that the consecutive measurements in univariate time-series contain information about the generating

process, which can be described by modelling the current value of the variable as a weighted linear sum of its previous values (Harrison et al., 2003). Connectivity is frequently assessed in terms of its Granger causality, that is, the amount of variance in one region that is explained by the signal history of another (Rogers et al., 2007). This may be valid provided the fMRI repetition time (TR) is less than about 2.5 s. Models can be bivariate, calculating the connectivity between each pair of regions. This could also be between a seed region and each individual voxel in the brain (Rogers et al., 2007). A potential problem in this method is that a common, possibly unmodelled, input might be driving the activity in both regions which are shown by this method to be causally connected (Goebel et al., 2003, Roebroeck et al., 2005). Alternatively a multivariate approach can be adopted, where the "unique" contribution one region makes to another is determined, taking all other associated regions into account (Harrison et al., 2003). Several other variations have also been devised to address this issue. (Harrison et al., 2003, Kaminski et al., 2001, Valdes-Sosa et al., 2004, Valdes-Sosa et al., 2005).

#### 1.4.4.5 Structural equation modeling (SEM):

SEM (also referred to as path analysis) is the most adaptable and commonly used approach to estimate effective connectivity analysis in fMRI (Buchel and Friston, 1997, Chaminade and Fonlupt 2003, Buchel et al., 1999, Toni, et al., 2002, Fletcher, et al., 1999, Goncalves, et al., 2001, Maguire, 2001, Honey et al., 2002, Mechelli et al., 2002, Kim et al., 2006), with multiple variations to address specific situations and limitations (Horwitz, 2003, Maguire, 2001, Kim et al., 2006). Using SEM there are some pitfalls which could lead to misleading conclusions, chief amongst them is that detailed anatomical knowledge about brain connections is required apriori (Whalley

et al., 2009).

#### 1.4.4.6 Volterra formulations:

Simple SEM models cannot deal with connections expressed in one context but not in another. Such non-linearity of response is believed to occur in the brain, and to take account of this in SEM 'Volterra formulations' can be used. For example, consider that the influence on one brain region has two components – a direct influence from a hierarchically lower region 'R1' on a higher region 'R2', and a modulatory influence from a super-ordinate brain region 'R3' on the effects of R1 on R2. By introducing a 'moderator' variable, which reflects the interaction between R1 and R2, SEM can accommodate Volterra formulations (Friston 2002, Whalley et al., 2009).

#### 1.4.4.7 Psychophysiological interaction maps (PPI maps):

PPI maps are a special case of SEM, where only one dependent variable is used to estimate its effective connectivity across the whole brain, by measuring the change in connectivity under changed experimental conditions. In other words, PPI estimates a stimulus-induced change in the influence of one brain region on another. A linear regression model is constructed, consisting of a seed voxel's time course, a stimulus-related signal change predictor and the interaction of the two terms, or the PPI (Rogers et al., 2007, Friston et al., 1997). PPIs are used to obtain whole brain connectivity maps, or PPI maps, from individual seed regions and have been used extensively (Boksman e al 2005, Taniwaki et al., 2003, Das et al., 2005).

As PPI is the method used in the present study, it's implementation has been discussed in greater detail in Chapter two, and further implications of using it to estimate connectivity has been elaborated in the general discussion.

## 1.5 Disconnection in Schizophrenia

Brain disorders have been associated with failures in brain connectivity as far back as far as Theodor Meynert (1833–1892) and Carl Wernicke (1848–1905). This was recently formalized in the disconnection hypothesis of schizophrenia, which posits that abnormality in connectivity, or degree of integration between different brain regions to perform a particular function, is a core part of the pathophysiology of schizophrenia (Friston, 1998, Stephan et al., 2009). Abnormal connectivity has been demonstrated in schizophrenia for varied functions including working memory (Bakshi et al., 2011), verbal tasks, saccadic variance, default mode network activity (reviewed in Van den Heuvel and Hulshoff Pol, 2010), emotion processing (Anticevic et al., 2011, Calhoun et al., 2009), and affect recognition (Fakra et al., 2008). Some of these are reviewed in Whalley et al., 2009.

Although connectivity in schizophrenia has been extensively investigated, comparing findings is complicated by methodological differences between studies, including connectivity measures, experimental task design, as well as medication and symptoms in patients (discussed further below). These methodological aspects, including seed selection procedures (Vul et al., 2009) and population size (Friston et al., 1999) have been suggested as very important influences on such analysis. Nevertheless, a strong trend of reduced connectivity in schizophrenia emerges (Pettersson-Yeo et al., 2011, Lynall et al., 2010).

As mentioned earlier in sections 1.2.3 and 1.3.3, disrupted fronto-temporal interactions might be a core feature of schizophrenia (Weinberger et al., 1992, Friston and Frith 1995, Volkow et al., 1988). The frontal and temporal structures

have been shown to be preferentially affected (Lawrie and Abukmeil 1998, Wright et al., 2000), numerous functional imaging studies have indicated abnormal fronto-temporal activation (e.g. Frith et al., 1995, Fletcher et al., 1999), and associated white matter tracts are generally shown to be affected (Wright et al., 2000, Petrides and Pandya 1988, Burns et al., 2003, Davis et al., 2003, Kubicki et al., 2003, Sigmundsson et al., 2001). However, it is not clear how this disruption might mediate the key features of schizophrenia (Konrad and Winterer 2007, Pettersson-Yeo et al., 2011).

The disconnection hypothesis suggests reduced functional integration, or functional disconnection, is a core feature of schizophrenia pathology (Friston, 1998). Here functional disconnection is defined as arising from abnormal plasticity, which is related to function of neurotransmitters, many of which are also associated with schizophrenia (Friston and Frith 1995, Friston, 1998, Friston 2002, Stephan et al., 2006, Stephan et al., 2009). This central role of neurotransmitters and synaptic plasticity has been suggested to also explain heterogeneous features of the disorder and varying presentation of symptoms, as well as the common late age of onset (Stephan et al., 2009). Several studies have shown functional disconnectivity in schizophrenia (Stephan et al., 2009, Lynall et al., 2010, Das et al., 2007, Craig et al., 2009) using a different methods of estimating connectivity and different psychological tasks. Some of these have been reviewed in Gur & Gur 2010, Whalley et al., 2009 and Schlösser et al., 2005. Some studies have shown that connectivity is not simply reduced in schizophrenia, but rather that a different pattern of connections are demonstrated (Skudlarski et al., 2010). Some studies have combined functional and anatomical connectivity analysis and shown both to be reduced in

synchronization (Camchong et al., 2009). Some studies have shown this reduced connectivity as regulation failure between cognitive and affective regions (Radulescu and Mujica-Parodi, 2008). Further, correlations between such disconnection and symptoms have also been investigated, but with no common conclusion (Schoen et al., 2010, Medkoure al., 2010). Finally, some studies have extended findings of abnormal functional connectivity to subjects at high risk of schizophrenia (Benetti et al., 2009, Li et al., 2010, Whalley et al., 2004 & 2005).

## 1.6 Genetic Factors in Schizophrenia and Connectivity

Schizophrenia is highly heritable (Meyer-Lindenberg and Weinberger, 2006), though it is not related to any one gene but an interaction of multiple genes (Harrison and Owen, 2003), in addition to environmental and epigenetic factors (Lisman et al., 2008). Polymorphisms in the genes encoding dysbindin, COMT, DISC1, RGS4, GRM3, G72, neuregulin-1, and the brain derived neurotrophic factor (BDNF) have been suggested as contributing towards a susceptibility to the disorder (Mei and Xiong, 2008, Harrison and Weinberger, 2005, Harrison and Owen, 2003, Hall et al., 2009).

Although BDNF is not the strongest candidate gene for schizophrenia, it is intrinsically connected with synaptic transmission and plasticity, which as mentioned in section 1.4.2 earlier, are key factors mediating connectivity. Therefore BDNF is a significant gene in light of the disconnection hypothesis of schizophrenia, which posits that connectivity is a core feature in the pathology of schizophrenia. Therefore the relation between genetic factors and schizophrenia might be mediated via inter-regional connectivity (Potkin et al., 2010, Whalley et al., 2005, Friston, 1998, Stephan et al., 2009, Stephan et al., 2006, Winterer et al., 2008). The associations between BDNF and schizophrenia are discussed in greater detail in the general discussion in Chapter seven.

BDNF is a neurotrophin, or growth factor, involved in synaptic plasticity and long term potentiation (LTP) (Poo 2001, Lu 2003), particularly in the hippocampus (Lu and Gottschalk 2000), insula (Escobar 2003) and anterior cingulate cortex (ACC) (Takahashi 2000, Lang et al., 2007), brain regions associated with emotion

and social function. BDNF is important for emotional learning (Hall et al., 2000, Rattiner et al., 2005), and BDNF deletion in the hippocampus effects memory (Heldt et al., 2007). These associations between BDNF and emotional function are discussed in greater detail in Chapter five.

Further, BDNF has been indicated as necessary for socially relevant learning, such as learning appropriate wariness of strangers after aversive social encounters (Berton and Nestler, 2005). In humans altered BDNF levels are found in situations of psycho-social stress (Castren et al., 2007, Hadjiconstantinou et al., 2001). These associations between BDNF and social function are discussed in greater detail in Chapter six.

Additionally, environmental factors are believed to play an important role in determining manifestation of disorder in those with genetic vulnerability. Stress, particularly socio-emotional, is a key environmental factor (Lawrie et al., 2008, Palomo et al., 2004, Howes et al., 2004, Benes et al., 1997) and social environment has been shown to affect manifestation and outcome of schizophrenia (Murphy and Raman, 1971). BDNF has also been related to the pathophysiology of stress (Colzato et al., 2011, Saruta et al., 2010), and therefore might be associated with individual differences in coping mechanisms in response to stress.

A functional polymorphism, val66met (rs6265), has been identified in the human BDNF gene, and in-vitro studies have shown that substitution of the met allele in this SNP diminishes activity-dependent secretion of BDNF (Egan et al., 2003, Chen et al., 2006). Due to the impact of BDNF on connectivity, this would predict a similar impact of the BDNF val66met SNP on connectivity, perhaps particularly related to affect and social cognition. Therefore the present study

investigates the effect of variation in the BDNF val66met SNP on connectivity, as described in Chapters five and six.

## 1.7 Amygdala as Hub in Social and Emotional Processing Networks

The amygdala is believed to detect the emotional or social salience of an input stimulus (Pessoa and Adolphs, 2010), especially when related to fear and threat, and accordingly modifying cognitive processing and behavioral output (Adolphs, 2001, Phelps and LeDoux, 2005, Anderson, 2007, Phillips et al., 2001) or learning (Gallagher and Holland 1994, Morrison and Salzman 2010, Ludmer et al., 2011, Holland and Gallagher 2004). This role has been shown in various studies (Morris et al., 1996, Suslow et al., 2006), both in cases of incidental and intentional perception, and in conscious and unconscious processing (Hall et al., 2004, Marco et al., 2005, Stein et al., 2007). There seems to be a lateralization effect to this role (Phillips et al., 2001, Baas et al., 2004).

Animal studies including in non-human primates, amygdala damage seems to reduce wariness of novel stimuli and also the animals' perceived approachability (Adolphs, 2001, Emery et al., 2001).

In humans, lesion studies have shown the amygdala is crucial for facial emotion recognition, particularly fear, and show impaired threat processing in individuals with bilateral amygdala damage, who were found to evaluate faces as more approachable than controls (Adolphs, 2001, Adolphs, Tranel and Damasio, 1998). Also human patients with amygdala damage demonstrate impaired experience of fear in response to threatening external stimuli (Feinstein et al., 2011).

Further, imaging studies show amygdala activation when subjects process fear-related facial expressions, and neutral expressions, in disorders such as social

phobia and schizophrenia (Adolphs, 2001, Morris et al., 1996, Birbaumer et al., 1998, Hall et al., 2004, Rauch et al., 2010).

Other social and emotional functions have also been associated with the amygdala (Fitzgerald et al., 2006, Bickart et al., 2010, Adolphs, Tranel & Damasio 1998, Adolphs 2002). The amygdala is a key hub in emotional networks particularly for fear processing (LeDoux, 1996, Allman and Brothers, 1994. The amygdala receives direct and indirect inputs (sub-cortical via thalamus, and cortical) from various sensory regions, connects to the hippocampus, and projects to motor regions such as lateral thalamus and periaqueductal grey (LeDoux, 2003, Amaral, 1992, LeDoux 1987). Other regions close to the amygdala including the temporal polar cortex and perirhinal cortex are also bi-directionally connected to it and therefore could form part of this network. The amygdala is also connected to cortical regions including the anterior cingulate cortex and orbitofrontal cortex (Krolak-Salmon 2004, Holland and Gallagher 2004) and these connections have also been implicated in schizophrenia (Benes, 2010). Imaging studies have as well confirmed the role of amygdala as a major hub in emotion processing networks (Stein et al., 2007, Marco et al., 2005) for both conscious and unconscious emotion processing.

Therefore given the role of disconnection in schizophrenia, prominence of social and emotional dysfunction in features of the disorder, and the focal role of the amygdala in social and emotional processing, a key question is whether the amygdala connectivity, particularly corresponding to socio-affective function, is impaired in schizophrenia, leading to impaired social and emotional behaviour.

## 1.8 Hypotheses for Present Study

Led by the past findings discussed above, in the present study I hypothesized abnormal fronto-temporal connectivity between control subjects and patients with schizophrenia in the psychological context of an emotion processing task involving fearful faces, as well as a social cognition based approachability judgment task. Further, I also hypothesized an association between BDNF, a candidate gene for schizophrenia, which also affects synaptic plasticity, and thereby connectivity. Specifically, that there would be significant fronto-temporal connectivity variation associated with the BDNF gene on the same two psychological tasks of fear processing and approachability judgment. These hypotheses are also presented in the table 1.8.1 below for clarity.

| | |
|---|---|
| a) Abnormal fronto-temporal connectivity between control subjects and patients with schizophrenia in the psychological context of: | i) an emotional processing task using fearful faces |
| | ii) a social cognition based approachability judgment task. |
| b) Significant fronto-temporal connectivity variation associated with the BDNF, a candidate gene for schizophrenia, which affects synaptic plasticity, in the same two tasks: | i) an emotional processing task using fearful faces |
| | ii) a social cognition based approachability judgment task. |

Table 1.8.1: Schematic Summary of Hypotheses

Based on the preceding discussion, I examined psychological context dependent effective connectivity using the psycho-physiological interaction method, and estimated effective connectivity from the amygdala, as an important hub in emotion and social networks, to the whole brain, and compared this between patients with schizophrenia and healthy controls. Further I also examined variation in this effective connectivity associated with the BDNF gene.

I intend to show that connectivity within the functional networks underlying emotional processing and social judgement are abnormal in schizophrenia, which might mediate the aberrant emotional and social behaviour seen in the disorder. Further, I intend to show that similar abnormalities are associated with variation of genes which have been associated with schizophrenia, as well as connectivity, representing a predisposition to features of the disorder.

## 1.9 Thesis Map and Chapter Organization

The following Chapters discuss the methods, results and conclusions of this study in greater detail. Chapter two describes the methods used. Chapters three and four describe the connectivity analysis for patients with schizophrenia versus healthy controls for fear processing, and during approachability judgments respectively. Chapters five and six describe the connectivity analysis for the met allele carriers versus val homozygotes of the BDNF val66met SNP, for fear processing and during approachability judgments respectively. Finally Chapter seven discusses the conclusions and implications of the results found.

The imaging data used in the present study was collected earlier, and some of them have already been published (Hall et al., 2008, Hall et al., 2010). In the present study I have used this data to extend previous analysis to examine the difference in connectivity between patients of schizophrenia and healthy populations, and in related genetic groups, as motivated in Chapter 1.8. Only the methodological details relevant to the current study (sections 2.1 to 2.5), and the analysis stages that were repeated for the present study (sections 2.6 and 2.7) have been discussed here, before presenting the analyses that was performed in the current study (sections 2.8 to 2.10).

Two different tasks were involved in the present study. The first analysed emotional processing using a task which studied implicit fear processing from facial images. This is henceforth referred to as the "fear task". The second analysed the processing of social cognition using a task which studied approachability judgement from faces. This is henceforth referred to as the "approachability task". The relevant

methods are introduced in Chapter two, focussing on the common elements. Each task and the relevant analysis is described in further detail in Chapters three to six.

# CHAPTER TWO: METHODS

## 2.1 Subjects

Twenty four patients meeting the DSM-IV diagnostic criteria for schizophrenia (American Psychiatric Association, 1994), were recruited for and scanned in this study. Of these, one was excluded due to existence of a benign cyst, and three had to be excluded for non-performance of the behavioural tasks in the scanner, as detected by monitored response times in the scanner. For the fear task only, one additional subject was excluded due to non-performance. Therefore the size of the patient population for the fear task was 19, whereas for the approachability task the size was 20 subjects.

In the fear task the 19 patients included in the analysis had an average age of 37.7 years (SD 8.4), and mean pre-morbid National Adult Reading Test (NART) of 111.6 (SD 10.1) There were 12 males in the patients group, and 17 were right handed. In the approachability task the 20 patients included in the analysis had a mean age of 33.4 years (S.D 12.3), mean pre-morbid NART IQ 111.1 (S.D 8.1) (Nelson and Willison, 1991).

All patients were treated with antipsychotic medication (16 with atypical anti-psychotics) with a mean chlorpromazine equivalent dose of 496mg (SD 377mg) and 494mg (SD 367mg) respectively for the patients included in the fear and approachability analysis respectively (Woods, 2003, Barr et al., 2010). Symptoms were rated on day of scanning, using Positive and Negative Syndrome Scale (PANSS) (Kay, et al., 1987) and these were used for correlation analysis (described in relevant sections of Chapters three to six).

Additionally 51 healthy subjects were recruited as controls from community contacts. Of these 24 subjects who matched the patient group were used in the patient

versus control analyses. Matched controls had an average age of 35.1 years (SD 9.7), and mean NART of 114.5 (SD 6.5). There were 16 males in the controls group, and all were right handed and Caucasian.

For the genetic analyses, only healthy subjects were used, to avoid medication confounds and due to smaller study numbers in patient group. Of the 51 recruited healthy subjects, some had to be excluded for factors including lack of active participation as identified during scanning, consent to use blood sample and ethnicity. The remaining 40 and 42 subjects were used in these analyses, for fear and approachability respectively. The demographics for the groups are detailed in Chapters three to six, for each individual analysis.

Exclusion criteria for patients were age under 18 or over 65 years, neurological disease or organic brain disease, dependence on alcohol or non-prescribed drugs and co-morbidity with other concomitant axis I or axis II disorder. Exclusion criteria for controls were the same as that of patients, with the additional criteria of a personal or family history of neurological or psychiatric disorder. Informed consent as approved by the Local Research Ethics Committee was obtained from all participants.

These details are summarised in tables 2.1.1 to 2.1.4 below. Further details of population are described in (Hall et al., 2008, Hall, et al., 2010), and the populations for each individual analysis are described in the appropriate sections in Chapters three to six.

| Group | Number | Age (SD) | NART (SD) | Males (Females) | Right Handed |
|---|---|---|---|---|---|
| Patients | 19 | 37.7 (8.4) | 111.6 (10.1) | 12 (7) | 15 (4) |
| Controls | 24 | 35.13 (9.7) | 114.6 (6.5) | 16 (8) | 24 (0) |

**Table 2.1.1 Demographic details of participants for the analysis of fear processing in schizophrenia**

| Group | Number | Age (SD) | NART (SD) | Males (Females) | Right Handed (Left Handed) |
|---|---|---|---|---|---|
| Patients | 20 | 37.5 (8.2) | 111.6 (9.8) | 12 (8) | 15 (5) |
| Controls | 24 | 35.13 (9.7) | 114.6 (6.5) | 16 (8) | 24 (0) |

**Table 2.1.2 Demographic details of participants for the analysis of approachability processing in schizophrenia**

| Group | Number | Age (SD) | NART (SD) | Males (Females) | Right Handed (Left Handed) |
|---|---|---|---|---|---|
| Val Homozygotes | 26 | 32.27 (8.2) | 116.5 (7.1) | 14 (12) | 25 (1) |
| Met Carriers | 14 | 28.6 (5.1) | 116.5 (6.7) | 7 (7) | 14 (0) |

**Table 2.1.3 Demographic details of participants for genetic analysis for fear processing**

| Group | Number | Age (SD) | NART (SD) | Males (Females) | Right Handed (Left Handed) |
|---|---|---|---|---|---|
| Val Homozygotes | 28 | 31.9 (7.9) | 116.4 (6.8) | 15 (13) | 27 (1) |
| Met Carriers | 14 | 28.6 (5.1) | 116.5 (6.7) | 7 (7) | 14 (0) |

**Table 2.1.4 Demographic details of participants for genetic analysis for approachability processing**

## 2.2 Genetic Analysis

The genetic analysis was done for the BDNF gene, as described in section 1.6. A functional polymorphism val66met, or SNP rs6265 (Egan et al., 2003) was genotyped.

The genotyping was done using genomic DNA isolated from a venous blood sample. The genotyping used standard TaqMan assays, by the TaqMan polymerase chain reaction (PCR) based method (TaqMan, AssayByDesign, Applied Biosystems, Foster City, California). This testing was conducted at the Wellcome Trust Clinical Research Facility, Edinburgh, United Kingdom (www.wtcrf.ed.ac.uk). Reproducibility of Taqman genotypes is typically 99.5%.

## 2.3 Behavioural Testing Outside the Scanner

### 2.3.1 Behavioural Testing Conducted Outside the Scanner alongwith the Fear Task

Following the scanning sessions, a standardized test of facial emotion recognition was conducted (Young, 2002). Facial images for ten people, taken from the Ekman and Friesen series (Ekman and Friesen, 1976), were used in this test. For each face, images corresponding to six basic emotions: happiness, surprise, fear, sadness, disgust, and anger (giving a total of 60 images, 10 for each emotion) were shown in randomized 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. Following this, computer generated images morphed between emotions likely to be confused were used to test of emotion recognition further (Sprengelmeyer et al., 1996, Young 2002). The names of the six emotions were displayed and participants were required to choose the appropriate responses by clicking the computer mouse. Additionally, standard tests for facial identity recognition were conducted using the 'Benton Test of Facial Recognition' (Benton et al., 1983). There was no time limit for responding. The next image was not shown until the subject had made a response. No feedback was given as to the appropriateness of any responses. These experimental tasks are further discussed in (Hall et al., 2008).

## 2.4 Experiment Design of Tasks in the Scanner

### 2.4.1 Experiment Design for the Fear Task

The imaging was performed using a block-design experiment, with three conditions: fear, neutral and baseline. During the fear blocks six faces from the Ekman and Friesen series (Ekman and Friesen, 1976) with a fearful emotional expression were presented for 3.5 seconds each, in a random order with a 0.5s inter-stimulus interval, and during the neutral blocks the same six faces showing a neutral emotional expressions were presented similarly. During baseline blocks participants were instructed to look at a fixation cross for 12.5 seconds. Fear and neutral blocks were alternated, each being presented three times, with the starting order counterbalanced across participants, and seven interleaved baseline blocks were shown with these. For both the fear and neutral conditions participants were required to select the gender of the facial image by pressing a button to select one of the alternate responses male or female displayed on the screen. Therefore in the fear condition subjects were responding to the fearful expression in the faces implicitly. Response time as well as within scanner behavioural measures where recorded (number of correct gender identifications made). These were used to control for non-participation in the task (as referred to in section 2.1) (Hall, et al., 2008, Hall, et al., 2010). Examples of the faces used, as well as the fixation cross for the baseline condition, are illustrated in figure 2.4.1 below.

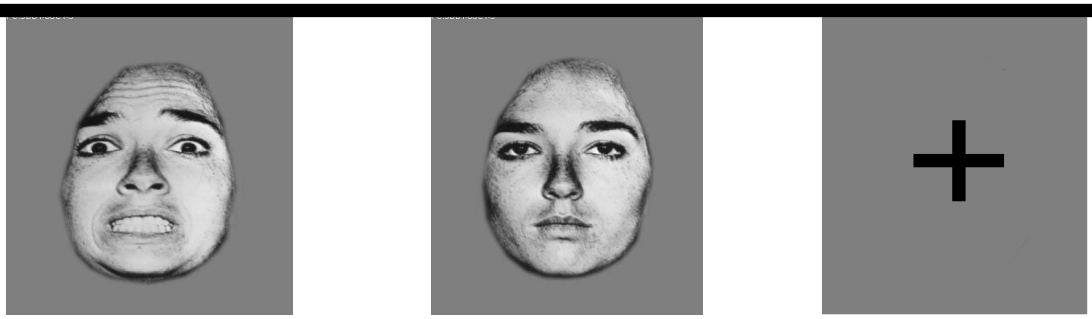


**Figure 2.4.1: Examples of Faces used for the Fear Task**

Examples of Ekman faces used for each of the blocks Fear and Neutral, followed by a diagram of baseline block (fixation cross). In Fear Blocks 6 faces with fearful expressions were shown (for 3.5 seconds each, in a random order with a 0.5s inter stimulus interval) and subjects were asked to indicate the gender of the face, therefore implicitly responding to the fearful expression. In the neutral condition the face used had a neutral expression, while everything else stayed the same.

**Figure 2.4.2: Examples of Faces used for the Approachability Task**

Three examples of non famous faces used for making approachability and gender judgements, followed by a diagram of baseline block (fixation cross). In approachability blocks 6 faces were shown (for 3.5 seconds each, in a random order with a 0.5s inter stimulus interval) and subjects were asked to indicate one of the choices 'approachable' or 'not approachable' shown on the screen below the image. The same face was shown in the gender condition, where the subjects were asked to indicate the gender of the face. The approachability minus gender contrast, considered here, therefore represents the neural response to explicitly processing the information in the face and making an approachability decision.

### 2.4.2 Experiment Design for the Approachability Task

In the approachability task, subjects were presented with facial images, and asked to rate the faces as 'very approachable' or 'not approachable'. The facial images were all of non-famous adults, derived from the media, and were previously rated for approachability by six volunteer participants. In a control condition subjects were asked to rate gender from the same faces.

The task consisted of two runs of six blocks per run, alternating blocks between approachability judgement (henceforth referred to as the approachability condition) and gender judgement (henceforth referred to as the gender condition), and the order of the blocks was counterbalanced across participants.

Each block was 25 second in duration, with each face presented for 3.5 s separated by a 0.5 s inter-stimulus interval (ISI). In between blocks were 12.5 second long baseline periods, during which participants were instructed to fixate on a cross in the centre of the screen. The dichotomized choices 'not approachable' and 'very approachable' were shown on the screen throughout the task. Participants had to press one of two buttons to choose an option. Responses were scored against the response most commonly assigned in the ratings study conducted previously, as described above, with a maximum score of 36 in each category. Response times were recorded for all judgements made in the scanner. These procedures are described in further detail in Hall et al., 2010. Examples of the faces used, as well as the fixation cross for the baseline condition, are illustrated in figure 2.4.2 above.

## 2.5 Imaging Acquisition

The fMRI image acquisition was performed using a GE 1.5 TE Sigma scanner (GE Medical, Milwaukee, WI, USA). Scanning was conducted at the SFC Brain Imaging Research Centre (BIRC) for Scotland. The imaging protocol constituted a localizer scan followed by a T2-weighted fast spin-echo sequence and a structural T1-weighted sequence. Finally, axial gradient echo-planar images (EPI), or functional imaging volumes were acquired (99 volumes; Field of View 22cm; Time to Echo (TE) 40ms; Volume acquisition time (TR) 2.5s; Interleaved acquisition order; axial slices were acquired with a thickness of 5mm with no gap and matrix size of 64 x 64). The first four EPIs were discarded to avoid T1 equilibrium effects (Hall et al., 2008, Hall et al., 2010).

## 2.6 Image Pre-processing

The acquired EPI images were first reconstructed offline in ANALYZE format (Mayo Foundation, Rochester, MN, USA). The resulting images were then pre-processed using the standard statistical parametric mapping (SPM) method in SPM2 (Wellcome Department of Cognitive Neurology and collaborators, Institute of Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm), written in Matlab Version 6.5.1.199709 Release 13 (The MathWorks, Natick, Massachusetts). Images from all subjects were inspected for susceptibility artefacts although none were excluded on that basis. Within-scanner movement data was examined for all subjects and no subject was found to have moved more than 3.0 mm in any axis across the duration of the scan.

The acquired EPI images were first spatially realigned to the mean volume in the time series to correct for head movement during volume acquisition. Subsequently the data was normalised to a standard stereotactic anatomical space and spatially smoothed using a Gaussian kernel (6 $mm^3$ full-width at half-maximum) to project the data onto a spatial scale such that homologies in functional anatomy can be found amongst subjects. Using SPM the entire series of transformations were individually estimated, but applied to the data in one reslicing step, thus reducing interpolation errors (Friston, 2002).

## 2.7 Image Analysis

Image analysis was performed using the standard statistical parametric mapping (SPM) method (Wellcome Department of Cognitive Neurology and collaborators, Institute of Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm), written in Matlab Version 6.5.1.199709 Release 13 (The MathWorks, Natick, Massachusetts). Statistical analysis was performed using the general linear model (GLM) approach as implemented in SPM2, to estimate the significant change in activity at each point across the whole brain volume, for each participant. The data for each task were modelled with three conditions (fear, neutral, baseline and approachability, gender, baseline for the fear and approachability tasks respectively, as described in the previous section) by a boxcar function and convolved with a canonical haemodynamic response function. Parameters representing the participant's movement during the scan were also entered into the model as covariates of no interest. Contrast images were generated for each participant for each contrast, representing the pair-wise comparison of parameter estimates between the individual conditions (fear versus neutral, fear versus baseline, neutral versus baseline and approachability versus gender, approachability versus baseline, gender versus baseline for the fear and approachability tasks respectively, as described in the previous section). These individual subject level results were used in random-effect group analysis using a two sample t-test (Penny et al., 2004) to derive the group level effects. These showed regions of significantly different activation between the groups corresponding to a contrast.

All statistical maps were thresholded at a level of $p < 0.005$ uncorrected, and regions were considered significant at $p < 0.05$ (cluster level, corrected for multiple

comparisons). The correction for multiple comparisons was performed by using cluster level correction in SPM. All co-ordinates were reported using the Montreal Neurological Institute (MNI) convention.

Only the 'fear versus neutral' contrast for the fear task, and the 'approachability versus gender' contrast for the approachability task, were chosen to be used for further analysis, as they represent the neural activation corresponding to implicit processing of the fearful emotion and explicit processing of approachability judgement respectively.

The coordinates of peak activation within each of the significantly activated clusters in each contrast were then reported as an estimate of neural response underlying the corresponding brain function, along with the corresponding p values at the corrected cluster level. Co-ordinates are given using the Montreal Neurological Institute (MNI) convention.

The brain region corresponding to this peak activation coordinate was examined using the Talairach Atlas, and also verified using the Talairach Daemon (Lancaster et al., 2000, Lancaster et al., 1997), WFU_PickAtlas v.2.0 (Tzourio-Mazoyer et al., 2002, Maldjian et al., 2003), Mango (http://ric.uthscsa.edu/mango) and MSU (www.ihb.spb.ru/~pet_la b/MSU/MSUMain.html) utilities. Further, the main regions that the cluster was found to extend over was also reported alongwith the peak activation region, for large clusters.

Region of interest analysis was conducted for the bilateral amygdala using a small volume correction (SVC) derived from the automated anatomical labelling atlas in WFU_PickAtlas v.2.0 dilated by 1 voxel to incorporate the full extent of the amygdala complex (Tzourio-Mazoyer et al., 2002, Maldjian et al., 2003). Further details are described in Hall et al., 2010.

## 2.8 Effective Connectivity Analysis

Effective connectivity is defined as 'the influence that one neural system exerts over another in the context of the current psychological context, as discussed in section 1.4. (Friston, 1995). Using the functional specialisation (section 1.3) results generated from fMRI studies that examine the multiple brain regions activated for an experimental task, connectivity is commonly estimated as statistical correlation between activation patterns in these distinct brain regions. A wide range of methods are used to calculate this statistical correlation. Here I used the Psychophysiological Interactions (PPI) method, where the change in connectivity from a chosen region to the rest of the brain is estimated, corresponding to a difference in psychological context. This is described in greater detail in section 2.8.1 below.

### 2.8.1 Psycho-physiological Interactions (PPI)

Psycho-Physiological Interaction (PPI) models connectivity from a chosen seed voxel to each voxel in the whole brain, corresponding to change in experimental condition. A diagrammatic example of principals behind PPI is demonstrated in figure 2.8.1 below. For the PPI analysis, the physiological term was estimated as the first eigenvariate time series from a 6 mm sphere volume of interest (VOI) at the seed, and the psychological term was estimated as the change of estimated brain activation between the experimental conditions of fear versus neutral, and approachability versus gender respectively, as described in the previous section. Hemodynamic De-convolution was performed on the extracted time series to remove the effects of canonical Hemodynamic Response Function (HRF). The resulting time-series were multiplied by the psychological variable and re-convolved with the HRF to obtain the

PPI interaction term using the PPI (spm_peb_ppi.m) SPM function (Gitelman et al., 2003).

All three terms were entered into a general linear model (GLM) using SPM2 (http://www.fil.ion.ucl.ac.uk/spm) to estimate the connectivity between the seed region and each voxel in the brain for each participant. In the GLM, the PPI term was the regressor of interest and the other two terms (psychological and physiological terms) were covariates of no interest (Friston et al., 1997). This analysis yielded one positive contrast image considering only the interaction term for each participant.

These individual subject level results were used in random-effect group analysis using a two sample t-test (Penny et al., 2004) to derive the group level effects. These showed regions of significantly different connectivity with the seed VOI between the groups, corresponding to the contrast of interest (described in the previous section). The coordinates of peak activation within each of the significantly activated clusters in each contrast were then reported as an estimate of the difference in connectivity between the two groups from the VOI, along with the corresponding p values at the corrected cluster level.

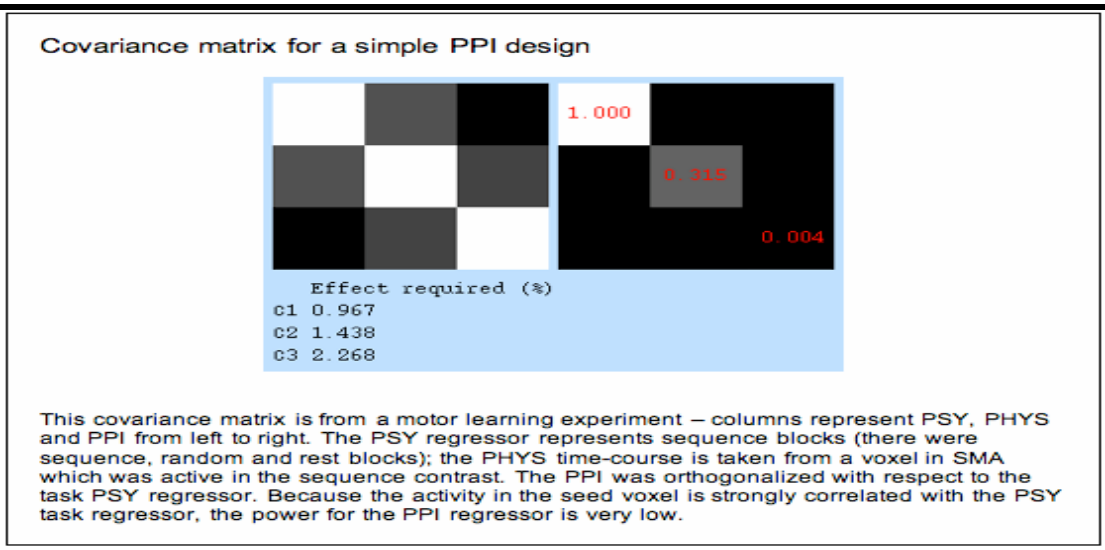
All statistical maps were thresholded at a level of $p < 0.005$ uncorrected, and regions were considered significant at $p < 0.05$ (cluster level, corrected for multiple comparisons). The correction for multiple comparisons was performed by using cluster level correction in SPM. All co-ordinates were reported using the Montreal Neurological Institute (MNI) convention.

The seed region was determined on the basis of peak activation in control subjects (for the fear and approachability tasks respectively) within an anatomically defined amygdala mask. This amygdala mask was generated using the wfu_pick atlas. The controls (at a group level) were used for this purpose as they might be assumed to

demonstrate the regions of normal amygdala activation for this cohort. The size of the region of interest was chosen as 6mm based on the smoothing kernel and the size of the anatomical region, and previous similar studies (Ide and Li, 2011).

The physiological term was extracted from the seed region as the first eigen variate of the BOLD signal for this anatomically defined amygdala ROI for each individual subject. This term denotes the average BOLD signal weighted by the voxel significance, which is more robust to outliers (Gitelman et al., 2003, Ide and Li, 2011), using the VOI extraction (spm_regions.m) SPM function (Friston et al., 1997). Hemodynamic Deconvolution was performed on the extracted time series to remove the effects of canonical Hemodynamic Response Function (HRF). The resulting timeseries were multiplied by the psychological variable and re-convolved with the HRF to obtain the PPI interaction term using the PPI (spm_peb_ppi.m) SPM function (Gitelman et al., 2003). The time series were not adjusted for any effects as confounds related to nuisance regressors would have already been factored into the previous stages of processing the data. The psychological term was the contrast of interest, as defined in the previous section. The psychological, physiological and interaction terms were entered into a whole brain GLM analysis. This was used to perform the PPI analysis for each subject, and generate positive contrast images considering only the interaction term (0 0 1) for each individual subject. These were then used in random-effect group analysis (Penny et al., 2004) to derive the group level difference. The entire procedure was implemented using SPM2 methods (Wellcome Department of Cognitive Neurology and collaborators, Institute of Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm), written in Matlab Version 6.5.1.199709 Release 13 (The MathWorks, Natick, Massachusetts), following standard procedures (McLaren, Personal Communication, Das et al., 2011, Fletcher et al., 1999, Mukherjee et al.,

2011, Ide and Li, 2011). These methods are discussed again, with specific details for each individual analysis, in Chapters three to six. Further implications and limitations of PPI are also discussed in the general discussion (Chapter seven).



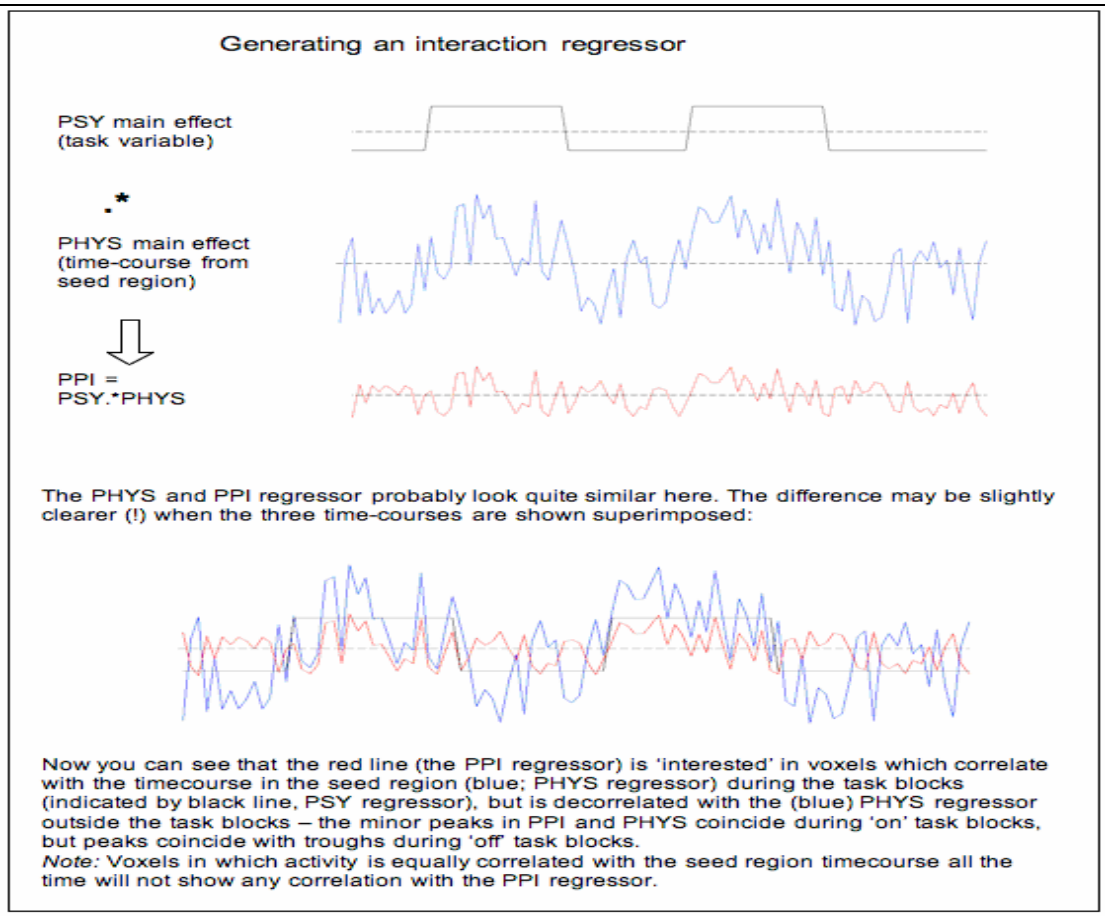




Figure 2.8.1 showing a covariance matrix for a simple PPI design and the psychological, physiological and interaction terms (Figure from: http://www.fmrib.ox.ac.uk/Members/joreilly)

## 2.9 Analysis of Behavioural Data

The mean response times with the scanner were recorded, for both the fear and approachability tasks, as described in section 2.4.

For the fear task, behavioural testing was performed outside the scanner, as described in section 2.3. For the approachability task within scanner behavioural data, as described in section 2.4.2, were analyzed.

These behavioural testing results were compared between the groups, using t-tests in SPSS (SPSS for Windows, version 14.0, SPSS Inc., US). These analyses have been described in greater detail in the relevant sections in Chapters three to six.

## 2.10 Symptom & Attribute Correlation Analysis

Correlations between the effective connectivity results and the symptom scores (measured using PANSS on day of scanning, as described in section 2.1) were analysed for the patient population, for both the Fear and Approachability task.

Effects of medication were investigated by calculating correlations between brain activations or connectivity results, with antipsychotic medication (chlorpromazine equivalent) dosage.

Correlations between the connectivity results and the subject population parameters or trait measures collected before scanning, including EQ (emotional quotient) and SQ (systemizing quotient) scores, were analysed for both the Fear and Approachability task.

These analyses were performed using bi-variate Pearson correlations in SPSS (SPSS for Windows, version 14.0, SPSS Inc., US), and have been described in greater detail in the relevant sections in Chapters three to six.

# CHAPTER THREE:

# Fear Processing in Schizophrenia

## 3.1 Introduction

As briefly described in Chapter one, many symptoms and deficits in schizophrenia can be related to social function (Frith et al., 1992). Two important aspects of social function are perceiving and processing emotional stimuli, such as fear, and making socially relevant judgements, such as the approachability of the other individual. Therefore in this chapter I have examined the effective connectivity differences in the distributed brain network for fear processing in individuals with schizophrenia. The behavioural and imaging data for the results in this chapter were collected earlier and separately published as Hall et al., 2008. The connectivity results (presented in this chapter) have been submitted for publication as (Mukherjee et al., submitted).

Schizophrenia is a severely debilitating disorder, with a complex clinical presentation. Patients suffer from a variety of positive and negative symptoms (Crow, 1980). Positive symptoms include delusional ideation, thought disorder, auditory and visual hallucinations, while negative symptoms include social withdrawal, lack of motivation, flattened affect (Frith, 1992). Many of these symptoms relate to social behavior and therefore social cognition has been suggested as a key function affected in schizophrenia (Brunet-Gouet and Decety, 2006, Burns, 2006, Couture et al., 2006, Lee et al., 2004, Baas et al., 2008a, Penn et al., 2006).

An important component of social cognition, processing emotion based on socially salient stimuli such as facial expressions, has been implicated in schizophrenia (as reviewed in Marwick and Hall 2008, Phillips et al., 2003, Ochsner et al., 2008, Earnst and Kring, 1999, Trémeau, 2006 and Mandal et al., 1998).

Processing facial emotion, particularly related to adverse emotions such as fear, has been extensively reported in schizophrenia (Bediou et al., 2007, Schneider et al., 2006, Bigelow et al., 2006, Johnston et al., 2008, Hall et al., 2008, Derntl et al., 2009, Chambon et al., 2006, Edwards et al., 2001, Edwards et al., 2002, Michalopoulou et al., 2008, and as reviewed in Morris et al., 2009. Further, these effects have been related to positive and negative symptoms such as paranoia and flat affect (Heimberg, et al., 1992, Van't Wout et al., 2007, Frith, 1992, Gur et al., 2007).

Another important area of social cognition is Theory of Mind (TOM), or thinking about other people's state of mind. Several studies have shown TOM processing to be impacted in schizophrenia (Ziv et al., 2011, Kosmidis et al., 2011, Bora et al., 2009, Sprong et al., 2007, Brune, 2005a, b, Harrington 2005, Frith, 2004). Further, neuropsychological studies have demonstrated similar TOM deficits in individuals at enhanced risk of schizophrenia, particularly in individuals who experienced psychotic symptoms at or around the time of testing.

The amygdala plays a key role in emotion processing, particularly for adverse emotions such as fear (Delgado et al., 2008, LeDoux, 2003, Morris et al., 1996, Ohman, 2005, Phelps, 2006, Calder et al., 2001, Adolphs, 2005). Patients with schizophrenia have shown both structural (Wright et al., 2000, Namiki et al., 2007, Shenton et al., 2001, Wright et al., 2000) and activation (Holt et al., 2006, Williams et al., 2007, Hall et al., 2008, Yamada et al., 2007, Baas et al., 2008b, Li et al., 2010, Gur et al., 2002, Anticevic et al., 2010, Pinkham et al., 2011) as well as connectivity (Benes 2010, Das et al., 2007, Williams et al., 2007) abnormalities associated with the amygdala (as reviewed in Aleman and Kahn, 2005, Kucharska-Pietura et al.,

2003 and Shayegan and Stahl, 2005). Fear related positive symptoms such as paranoia have also been associated with abnormal amygdala function (Russell et al., 2007, Williams et al., 2007, Williams et al., 2004, Taylor et al., 2002). Due to the associations between the amygdala and recognition of emotional expressions and internal response in response to emotional experience, it has also been connected to negative symptoms such as anhedonia and flattened affect (Davis and Whalen, 2001, Ochsner et al., 2008).

In an earlier study we demonstrated that compared to healthy subjects, patients with schizophrenia showed significantly different amygdala activation. Whereas patients under-activated the amygdala while viewing faces with fearful expressions, as compared to the viewing the same faces with neutral expression, they over-activated the amygdala while viewing the faces with neutral expression, as compared to the baseline condition (Hall et al., 2008). This might correspond to patients over expressing fear reaction to non-fearful stimuli as suggested (Ochsner et al., 2008) and might correspond to dys-regulation of amygdala response to stimuli once it has been found non-fearful (Ochsner et al., 2008, Whalen, 1998).

Altered structural (Konrad and Winterer, 2008) and functional connectivity (Whalley et al., 2009, Brown and Thompson, 2010, Stephan et al., 2006, Pettersson-Yeo et al., 2011) have been extensively reported in schizophrenia, and connectivity has been suggested as being a core pathological factor (Friston, 1998). While increased connectivity has been shown in some studies (Salgado-Pineda et al., 2010; Satterthwaite, et al., 2010), most studies have reported reduced connectivity between task relevant network nodes in patients with schizophrenia (Fletcher et al., 1999,

Lawrie et al., 2002, Raymond et al., in press, Salgado-Pineda et al., 2010, Satterthwaite et al., 2010, Stephan et al., 2006, Wolf et al., 2007, Zhou et al., 2007), including for processing negative emotion such as fear (Williams et al., 2007, Modinos et al., 2010, Das et al., 2007). It has been suggested that increased connectivity found in some studies might be a compensatory mechanism in patients (Wolf et al., 2007). In our earlier study we found indications of lower connectivity for fear processing between the amygdala and fusiform gyrus in patients with schizophrenia using a simple Pearson correlation based approach (Hall et al., 2008).

In the present study, I examined the effective connectivity from the amygdala to the whole brain, corresponding to processing fearful facial expressions as compared to neutral expressions, and compare this between patients of schizophrenia and control participants. I hypothesized that patients with schizophrenia would show abnormal connectivity between the amygdala within components of the distributed network for fear processing (Liddell et al., 2005; Stein et al., 2007). I suggest this network dysfunction might contribute to behavioral abnormalities in social cognition in patients with schizophrenia.

## 3.2 MATERIALS AND METHODS

### 3.2.1 Participants

Participants included 24 patients meeting DSM-IV diagnostic criteria for schizophrenia (Hall et al., 2008). Exclusion criteria were age under 18 or over 65, neurological disease, other psychiatric disorder and dependence on alcohol or non-prescribed drugs. One participant was excluded due to the presence of a benign cerebral cyst and four individuals due to a failure to make any behavioral responses in the scanner.

The remaining 19 individuals in the patient group were all Caucasian and all were treated with antipsychotic medication (16 with atypical anti-psychotics) with a mean chlorpromazine equivalent dose of 496mg (SD 377mg) (Woods, 2003, Barr et al., 2010). Symptoms were rated on the day of the scanning session using the positive and negative syndrome scale (PANSS) and the mean PANSS score was 23.1 (SD 5.3). Mean positive syndrome score on the PANSS was 12.3 (SD 4.5) with 15 out of the 19 individuals scoring three or greater on one or more positive syndrome items. Mean negative syndrome score on the PANSS was 11.8 (SD 3.4).

Additionally, 24 healthy control volunteers were recruited from the same regions and communities as the patients themselves. All control participants were Caucasian and right handed. Control participants had the same exclusion criteria as the patients, with the addition of any family or personal history of psychiatric illness.

Subject population trait measures were collected before scanning, including EQ (emotional quotient) and SQ (systemizing quotient) scores. Local ethics approval

was obtained and all participants gave informed consent. Detailed demographics are shown in table 3.3.1.

### 3.2.2 Behavioural Testing Outside the Scanner

Following the scanning sessions, a standardized test of facial emotion recognition was conducted, as described in Chapter two.

### 3.2.3 Experimental Design

Functional imaging was performed using a block-design experiment, with three conditions: fear, neutral and baseline. During the fear blocks six faces from the Ekman and Friesen series (Ekman and Friesen 1976) with a fearful emotional expression were presented for 3.5 seconds each, in a random order with a 0.5s inter-stimulus interval, and during the neutral blocks the same six faces showing a neutral emotional expression were presented similarly. During baseline blocks participants were instructed to look at a fixation cross for 12.5 seconds. For both the fear and neutral conditions participants were required to select the gender of the facial image. Response time as well as within scanner behavioural measures where recorded (number of correct gender identifications made). These were used to control for non-participation in the task.

### 3.2.4 Imaging

The fMRI image acquisition was performed as described in Chapter two.

### 3.2.5 Image Analysis

The acquired images were analysed. Details are described in Chapter two.

### 3.2.6 Connectivity Analysis

Connectivity analysis was performed using psycho-physiological interaction (PPI), as described in Chapter two.

### 3.2.7 Correlation of Connectivity in Patients with Symptoms

A post-hoc comparison of the correlation of abnormal effective connectivity in patients with their symptoms was performed. This was done by extracting the first eigenvariate time series from a 6mm sphere volume of interest (VOI) at the tempero-parietal junction (TPJ) from the PPI connectivity spm. This factor was correlated with related PANSS symptom scores using the SPSS software (SPSS for Windows, version 14.0, SPSS Inc., US), using Pearson correlations. The PANSS positive and negative subscale totals were considered for this analysis.

## 3.3 RESULTS

### 3.3.1 Demographics

There were no significant differences found between individuals with schizophrenia and healthy controls in age ($F_{1,41} = 0.9$, $p = 0.3$), National Adult Reading Test (NART) IQ ($F_{1,41} = 1.3$, $p = 0.2$) or gender (Fisher's Exact Test, $p = 1.0$) as shown in table 3.3.1 below.

### 3.3.2 Difference in Emotional Behaviour between Groups

Within scanner behaviour measures (reaction time and gender discrimination) showed a high degree of accuracy (patients 91% correct, SD 13%, control subjects 98% correct, SD 3%) amongst participants who performed the task in the scanner, although the patients showed a deficit in accuracy of gender judgments compared with control subjects ($F_{1,41} = 6.4$, $p < 0.05$).

Tests of emotion recognition using Ekman faces, conducted outside the scanner as described in 3.2.1 above, was compared between patients and healthy controls using an ANOVA with group as a between-subjects factor and emotion as a within-subjects factor. These showed a significant overall effect of group ($F_{1,41} = 7.0$, $p = 0.010$) and emotion ($F_{5,205} = 32.1$, $p < 0.001$) and a trend to a group-by-emotion interaction ($F_{5,205} = 2.2$, $p = 0.054$) as shown in figure 3.3.1 below. Post-hoc t tests showed a significant impairment in the recognition of the emotion of fear in patients with schizophrenia relative to control participants ($p < 0.01$).

| Group | Number | Age (SD) | NART (SD) | Males (Females) | Right Handed (Left) |
|---|---|---|---|---|---|
| Patients | 19 | 37.7 (8.4) | 111.6 (10.1) | 12 (7) | 15 (4) |
| Controls | 24 | 35.13 (9.7) | 114.6 (6.5) | 16 (8) | 24 (0) |

**Table 3.3.1 Demographic Details of Patients and Controls for Fear Task**

This table shows the demographic details of all the participants included in this analysis including the individuals with schizophrenia (patients) and the healthy control participants (controls).

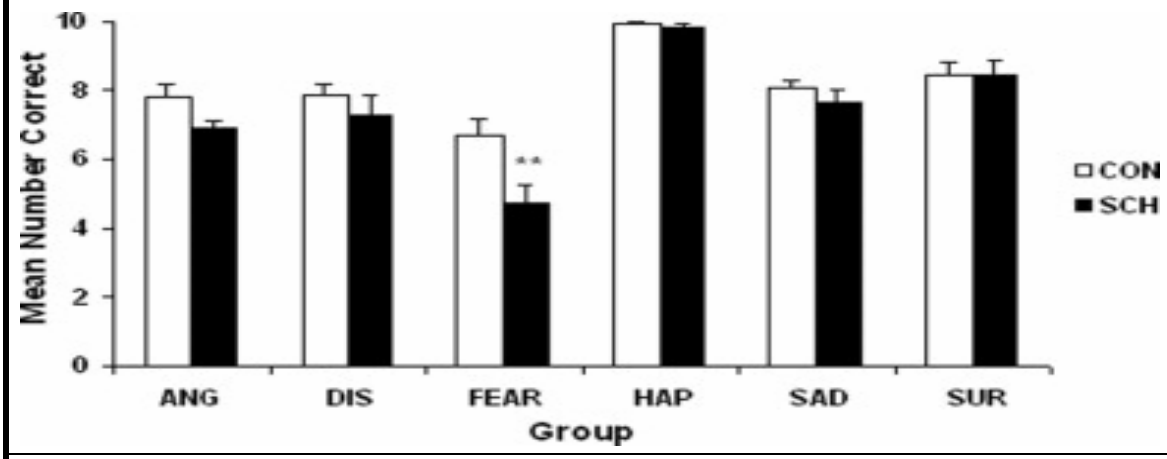



**Figure 3.3.1 Results of Behaviour Testing Outside the Scanner Patients and Controls alongwith Fear Task**

This figure shows the results of the behaviour testing conducted outside the scanner for all the participants included in this analysis including the individuals with schizophrenia (SCH) and the healthy control participants (CON). This testing was conducted using Ekman faces for the six basic emotions Anger (ANG), Disgust (DIS), Fear, Happiness (HAP), Sadness (SAD) and Surprise (SUR). The details of the analysis are described above.

### 3.3.3 Neural Response to Fear in Healthy Participants

Considering only the healthy participants together, to demonstrate normal activation, a cluster located within peak activation in the middle temporal gyrus ($p_{corr}$ = 0.006, $K_E$ = 706, Peak T = 5.12, coordinates = 58, -64, 8), a cluster with peak activation in the right fusiform gyrus ($p_{corr}$ < 0.001, $K_E$ = 1277, Peak T = 4.55, coordinates = 34, -72, -16) and a cluster with peak activation in the left cerebellum ($p_{corr}$ < 0.001, $K_E$ = 1500, Peak T = 4.47, coordinates = -36, -76, -20) were found significantly overactivated in the fear versus neutral contrast, at threshold $p < 0.005$. This is shown in appendix table 1 and appendix figure 1.

### 3.3.4 Reduced Neural Response Individuals with Schizophrenia

All 19 individuals with schizophrenia who performed the task in the scanner showed expected patterns of activation based on earlier studies. For the fear versus neutral contrast, comparing brain activation between the patients and healthy controls, patients showed significantly lower activation in a cluster located within the right lingual gyrus ($p_{corr}$ < 0.001, $K_E$ = 4190, Peak T = 4.48, coordinates = 20, -78, -2) and another in the right superior temporal gyrus ($p_{corr}$ = 0.015, $K_E$ = 730, Peak T = 4.23, coordinates = 58, -16, 4). Further, using a SVC for the amygdala patients showed reduced activation in the left amygdala ($p_{corr}$ = 0.039, $K_E$ = 102, Peak T = 3.59, coordinates = -22, 0, -14). These results are shown in table 3.3.2 and figure 3.3.2 below.

| $p_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| < 0.001 | 4190 | 4.48 | 20, -78, -2 | Right lingual gyrus |
| 0.015 | 730 | 4.23 | 58, -16, 4 | Right superior temporal gyrus |
| 0.039 | 102 | 3.59 | -22, 0, -14 | Left amygdala (with SVC) |

**Table 3.3.2 Regions Showing Reduced Activation in Patients (Fear Task)**
This table shows the regions with significantly reduced activation in patients, for the fear versus neutral contrast, thresholded at p < 0.005, uncorrected.

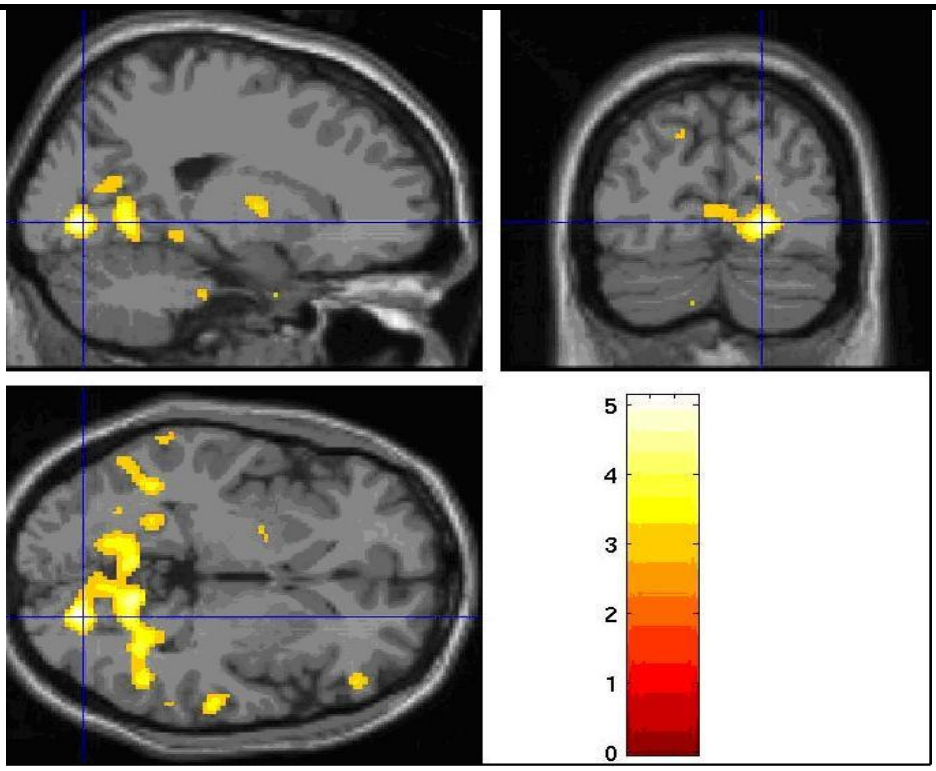



**Figure 3.3.2 Regions with Reduced Activation in Patients (Fear Task)**
This figure is a SPM illustrating the regions with reduced neural activation in patients with schizophrenia, compared to healthy controls, for the fear versus neutral contrast, The figure is a statistical parametric map (SPM) with regions with significantly decreased activation shown in yellow, thresholded at p < 0.005, uncorrected. The cross hairs are at MNI coordinates 20, -78, -2

### 3.3.5 Amygdala Connectivity in Healthy Participants

Within the healthy controls, there were no significant differences in connectivity from the bilateral amygdala seeds to the whole brain between the fear and neutral conditions.

A post-hoc exploratory analysis of the difference in connectivity between the fear and neutral conditions, however, from the left amygdala seed (peak MNI coordinates -26, 0, -20) to the whole brain showed the region with significantly reduced connectivity in the patients, discussed in the following section, were also recruited by the control subjects (a region extending over the tempero-parietal junction, MNI coordinates 34, -66, 48, inferior parietal lobe, superior temporal gyrus and precuneus), although these differences did not reach statistical significance.

### 3.3.6 Reduced Connectivity in Individuals with Schizophrenia

Compared to healthy controls, the results showed patients with schizophrenia had significantly decreased effective connectivity corresponding to the fear versus neutral contrast, from the left amygdala seed (peak MNI coordinates -26, 0, -20) to a large cluster extending over the right tempero-parietal junction ($p_{corr} < 0.001$, $K_E = 1511$, Peak T = 7.73, coordinates = 50, -48, 52), inferior and superior parietal lobe (BA 40) and superior and middle temporal gyrus, supra-marginal gyrus and the precuneus. There were no significantly overactivated regions between the two groups in the reverse contrast, or from the right amygdala. These results are shown in table 3.3.3 and figure 3.3.3 below.

| $p_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| < 0.001 | 1511 | 7.73 | 50, -48, 52 | Temporo-Parietal Junction (TPJ) |

**Table 3.3.3 Reduced Connectivity in Patients (Fear Task)**

This table shows the regions with significantly reduced effective connectivity with the left amygdala, in patients compared to controls, for the fear versus neutral contrast, thresholded at $p < 0.005$, uncorrected.

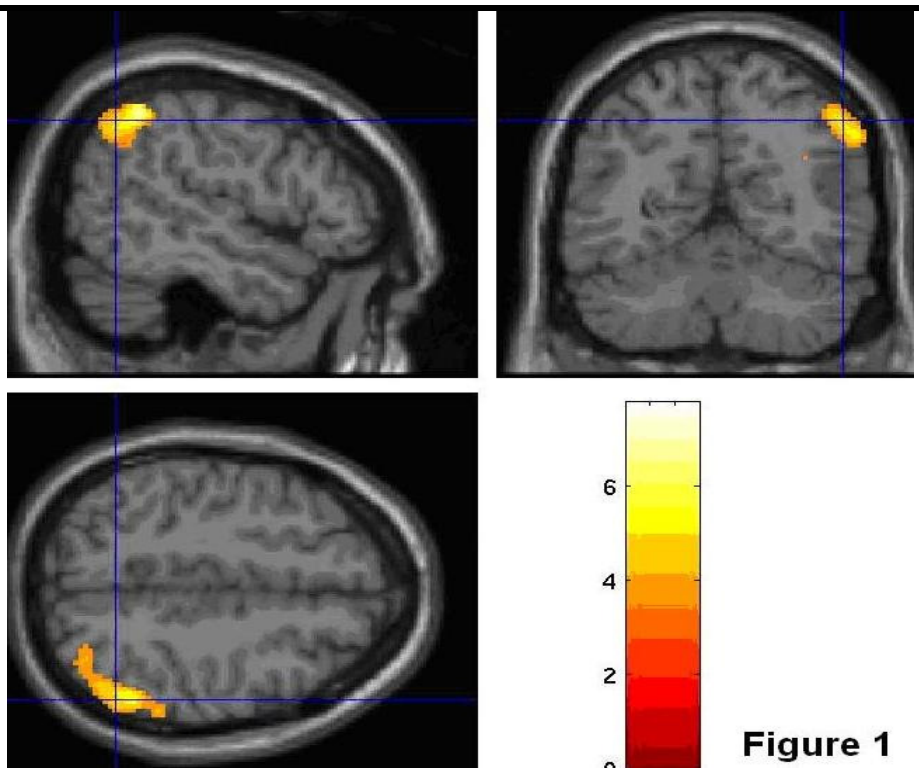



**Figure 3.3.3 Reduced Connectivity in Patients (Fear Task)**

This figure is a SPM illustrating the regions with reduced effective connectivity from the left amygdala in patients with schizophrenia, compared to healthy controls, for the fear versus neutral contrast, in yellow, thresholded at $p < 0.005$, uncorrected. The cross hairs are at MNI coordinates 50, -48, 52

### 3.3.7 Correlation of Connectivity with Behaviour and Traits

Correlation analysis was performed to assess whether connectivity calculated above was related to trait measures SQ and EQ. Further, correlation analyses were also performed to assess whether connectivity was related to measures of within scanner gender judgment performance or response times for all participants. Finally, correlation analyses was performed to assess whether connectivity was related to measures of behavioral testing for ability to recognize emotional expressions from faces, conducted outside the scanner for all participants. None of these correlations were significant.

### 3.3.8 Correlation of Connectivity with Symptoms in Patients

Correlation analyses were performed to assess whether connectivity was related to the symptoms in patients. The PANSS total score, PANSS positive or PANSS negative symptoms were used for this analysis and no significant correlations were found.

On further exploratory testing of correlation with items, however, a significant correlation was found with the PANSS negative score for abstract thinking ($p = 0.021$, $r = 0.524$), but this would not survive correction for multiple hypothesis testing.

### 3.3.9 Correlation of Connectivity with Antipsychotic Dose

Correlation analysis was performed to assess whether connectivity calculated above was affected by antipsychotic medication dosage of chlorpromazine equivalents (Barr et al., 2010, Woods 2003). No significant correlations were found.

## 3.4 Discussion

In the present study I showed reduced effective connectivity between the amygdala and regions including the precuneus and TPJ, corresponding to viewing fearful, as compared to neutral faces, in patients with schizophrenia, compared to healthy subjects.

The amygdala is key to fear processing (LeDoux 2003), and is believed to act as a vigilance system, evaluating salience of threat related stimuli (Davis and Whalen, 2001, Ochsner et al., 2008). The Amygdala has been repeatedly implicated in schizophrenia, as reviewed in Aleman and Kahn, 2005, Kucharska-Pietura et al., 2003 and Shayegan and Stahl, 2005.

The TPJ is involved in high level social cognition (Decety and Lamm, 2007), particularly TOM, or thinking about another individual's state of mind (Saxe and Powell, 2006, Brass et al., 2005, Perner et al., 2006, Saxe, 2006, Saxe and Kanwisher, 2003, Young and Saxe, 2008, 2009a, b), mentalizing or 'perceiving and reasoning about other people' and processing mental representations about other people (Saxe and Kanwisher 2003, Brass et al., 2005, Perner et al., 2006, Saxe 2006, Young and Saxe 2008, Young and Saxe 2009), as well as directing attention Robertson et al., 1988. Functional abnormalities in the TPJ were reported in studies of empathy and theory of mind in schizophrenia (Benedetti et al., 2009, Vistoli et al., 2011). The precuneus, as well as the TPJ, is also associated with as mentalizing and theory of mind (Mar, 2011, Fletcher at al., 1995b).

Functional disconnection has been suggested as a root etiological factor in schizophrenia (Friston, 1998), contributing to abnormal behaviour related to

emotional and social function (Allman et al., 2001). Interestingly, in the context of connectivity, studies modelling whole brain connectivity have shown the precuneus to be one of the major connectivity hubs in the brain (Tomasi et al., 2010, Tomasi et al., 2011). Additionally, network simulation studies found that lesions in the TPJ were more disruptive to overall connectivity in models, compared to other regions (Alstott et al., 2009), which implies this region too is an important connectivity hub in the brain. Further, the amygdala also has known connections to distributed brain regions, and is believed to play a central role the socio-affective functional network (Phelps and LeDoux, 2005).

Therefore, in the light of all the associations mentioned above, the reduced effective connectivity between Amygdala and TPJ corresponding to processing fearful facial expressions shown in schizophrenia in the present study might illustrate disconnection between brain regions associated with emotions, particularly aversive emotions such as fear, and brain regions involved in more advanced social function such as thinking about other people. This disconnection might be a factor contributing towards fear related social behaviour seen in schizophrenia.

As discussed in Chapter One, social behaviour abnormalities are a central feature of schizophrenia (Frith, 1992). Emotion processing, particularly for aversive emotions such as fear (Phillips et al., 2003, Ochsner et al., 2008, Earnst and Kring, 1999 and Trémeau, 2006), can be associated with many of the features and symptoms of the disorder. Further, theory of mind related abnormalities have also been shown in schizophrenia (Corcoran 2001, Hall et al., 2004, Lee, et al., 2004, Brune 2005, Brune 2005, Brunet-Gouet and Decety 2006, Burns 2006, Bora et al.,

2009). Making social judgements from faces, such as making inferences about another individual's internal state of mind, are important components of social function (Hooker and Park 2002). Dysfunction in such facial emotion processing capacities have been extensively reported in schizophrenia (Marwick and Hall 2008, Phillips et al., 2003, Ochsner et al., 2008, Earnst and Kring, 1999, Trémeau, 2006 and Mandal et al., 1998, Bediou et al., 2007, Schneider et al., 2006, Bigelow et al., 2006, Johnston et al., 2008, Hall et al., 2008, Derntl et al., 2009, Chambon et al., 2006, Edwards et al., 2001, Edwards et al., 2002, Morris et al., 2009), particularly for negative emotions such as fear (Michalopoulou et al., 2008), as described in the introduction. Further, these deficits have been related to positive and negative symptoms such as paranoia and flat affect (Heimberg, et al., 1992, Van't Wout et al., 2007, Frith, 1992, Gur et al., 2007).

Thinking about other people's state of mind, or TOM, has been extensively shown as impacted in schizophrenia (Ziv et al., 2011, Kosmidis et al., 2011, Bora et al., 2009, Sprong et al., 2007, Brune, 2005a, b, Harrington 2005, Frith, 2004).

In conclusion the results of the present study illustrate an instance of functional disconnection for fear processing, between regions associated with fear and theory of mind, both behaviours impacted in schizophrenia. This might be a factor contributing to some of the abnormal social behaviours or function found in schizophrenia. It does not however appear to be related to psychotic symptoms in the present study.

The potential explanations of this reduced effective connectivity are considered in detail in the general discussion in Chapter seven.

A limitation of the present study is that I have examined a specific type of effective connectivity which indicates the change in influence of a neuronal system over another, for a change psychological context, but does not indicate if this relationship is causal (Friston, et al., 1998). Additionally, I have not investigated any related structural connectivity. Finally, there might be a possible influence of antipsychotic medication in patients on synaptic plasticity (Stephan et al., 2001), although no evidence was found of a correlation between effective connectivity and medication dose.

# CHAPTER FOUR:

# Approachability Judgement in Schizophrenia

## 4.1 Introduction

As described in Chapter 1, many symptoms and deficits in schizophrenia relate to social function (Frith et al., 1992). One of the most important aspects of social function are perceiving emotional and other stimuli, and making socially relevant judgements, such as the approachability of the other individual (Penn et al., 2008). In this chapter I have examined the neural activation and effective connectivity differences in the distributed brain network which underlie making approachability judgements in individuals with schizophrenia compared to controls. The imaging data in this chapter were collected earlier (not as part of the present study), and the brain activation data for the controls only was separately published as Hall et al., 2010. The abnormalities found in neural activation and effective connectivity for this task in individuals with schizophrenia, compared to healthy controls, are presented in this chapter.

Social cognition plays a key role in schizophrenia as many positive and negative symptoms, such as delusions of persecution and withdrawal, relate to abnormal social interactions (Baas et al., 2008a, Brunet-Gouet and Decety, 2006, Burns, 2006, Lee et al., 2004, Frith, 1992). Deficits in interpreting social cues, such as facial emotions (Penn et al., 2008, Marwick and Hall, 2008, Mandal et al., 1998, Edwards et al., 2001, Edwards et al., 2002) have been demonstrated in schizophrenia. Individuals with schizophrenia have been found to be impaired in making complex social judgements from facial emotional stimuli (Penn et al., 2008, Hooker et al., 2011), even when they showed no deficits in face recognition (Baas et al., 2008a),

and during assessment of non-emotional attributes of the facial stimuli, such as age or gender (Schneider et al., 2006). Additionally, impaired social behaviour has been shown to correlate with symptoms such as paranoia (Pinkham et al., 2011) and persecutory delusions (Haut and MacDonald, 2010, Hooker et al., 2011).

A distributed network of brain regions has been associated with social cognition in healthy individuals (Adolphs, 2001, Brothers, 1990) both for processing basic information from faces (Haxby et al., 2000), and making more complex social judgements (Hall et al., 2010, Saxe, 2006, Winston et al., 2003). The amygdala is a major hub in this social brain network (Phelps and LeDoux, 2005, Amaral, 1992) and is associated with evaluating the emotional salience of social stimuli (Davis and Whalen, 2001). Additionally, individuals with bilateral amygdala damage show deficits in wariness of unfamiliar people (Adolphs et al., 1998). Further, the orbitofrontal cortex (OFC), medial prefrontal cortex (MPFC), fusiform gyrus (FG), inferior frontal gyrus (IFG), the superior temporal sulcus (STS) have also been associated with social judgement (Willis et al., 2010, Amadio and Frith, 2006, Haxby et al., 2000, Kemmotsu, et al., 2005, Allison et al., 2000).

Many of the regions involved in social cognition, including the amygdala, MPFC, STS and FG have been implicated in schizophrenia (Li et al., 2010, Pinkham et al., 2003, Hall et al., 2004, Lee et al., 2004). Both structural and functional abnormalities have been demonstrated in the amygdala in individuals with schizophrenia (for review, see Aleman and Kahn, 2005, Shayegan and Stahl, 2005 and Kucharska-Pietura et al., 2003).

One possible underlying cause of the distributed deficits of the social brain found in schizophrenia is aberrant connectivity between the different brain regions associated with social cognition (Burns et al., 2003, Lee et al., 2004), particularly fronto-temporal connectivity (Friston and Frith 1995, Volkow et al., 1988). Functional disconnection was first suggested as a key etiological factor in schizophrenia by Friston, 1998. Subsequently several studies have reported altered connectivity in schizophrenia (as reviewed in Calhoun et al., 2009, Gur and Gur 2010, Whalley et al., 2009, Stephan et al., 2009 and Schlösser et al., 2005). Social cognition is suggested as having subsidiary components including emotion processing, theory of mind, and social judgement (Lieberman, 2007). Although connectivity has been examined from the amygdala for fear and other emotion processing (Anticevic et al., 2011, Calhoun et al., 2009), as well as for face identity and affect recognition (Fakra et al., 2008) and functional activation differences have been shown for higher level social judgement such as trustworthiness (Baas et al., 2008a, Pinkham et al., 2011), and theory of mind (Bozikas et al., 2011, Vistoli et al., 2011, Kim et al., 2011) any abnormal connectivity for such higher level social judgements has not as yet been shown in schizophrenia at the time of writing, to my best knowledge. Connectivity for social cognition has, however, been extensively investigated in health, indicating the networks usually recruited, as well as in diverse disorders such as autism spectrum disorder and post traumatic stress disorder, also associated with abnormal social behaviour demonstrating abnormal connectivity.

In the present study I hypothesized that the social cognition impairments seen in schizophrenia derive from disconnection within the neuronal network for social

cognition. In order to test this hypothesis I compared brain activation, as well as the effective connectivity from the amygdala to the whole brain, corresponding to an important social cognition function of making approachability judgments from faces, between individuals with schizophrenia and healthy individuals.

## 4.2 MATERIALS AND METHODS

### 4.2.1 Participants

Participants included 24 patients meeting DSM-IV diagnostic criteria for schizophrenia. Exclusion criteria were age under 18 or over 65, neurological disease, other psychiatric disorder and dependence on alcohol or non-prescribed drugs. One participant was excluded due to the presence of a benign cerebral cyst and three individuals due to a failure to make any behavioral responses in the scanner.

The remaining 20 individuals in the patient group were all Caucasian and all were treated with antipsychotic medication (16 with atypical anti-psychotics) with a mean chlorpromazine equivalent dose of 494mg (SD 367mg) (Woods, 2003, Barr et al., 2010). Symptoms were rated on the day of the scanning session using the positive and negative syndrome scale (PANSS) and the mean PANSS score was 22.7 (SD 5.1). Mean positive syndrome score on the PANSS was 12.3 (SD 4.5) with 15 out of the 20 individuals scoring three or greater on one or more positive syndrome items. Mean negative syndrome score on the PANSS was 15.8 (SD 4.2).

Additionally, 24 healthy control volunteers were recruited from the same regions and communities as the patients themselves. All control participants were Caucasian and right handed. Control participants had the same exclusion criteria as the patients, with the addition of any family or personal history of psychiatric illness.

Subject population trait measures were collected before scanning, including EQ (emotional quotient) and SQ (systemizing quotient) scores. Local ethics approval

was obtained and all participants gave informed consent. Detailed demographics are shown in table 4.2.1.

### 4.2.2 Experimental Design

Neural processing for social cognition during a task which targeted approachability judgment from faces was compared between both groups. The task consisted of three conditions: approachability, gender and baseline (see figure 4.2.1 below). In the approachability condition, participants were presented with facial images and asked to rate the faces as 'very approachable' or 'not approachable'. The facial images were of non-famous adults previously rated for approachability by separate healthy volunteers (for further details, see chapter 2). In the gender condition, participants were asked to indicate the gender from the same facial images as used in the approachability condition. During baseline blocks participants were instructed to look at a fixation cross for 12.5 seconds. The task had a consisted of two runs of six blocks each, alternating blocks between approachability judgment and gender judgment, with the order of the blocks being counterbalanced across participants. Each block was 25 seconds in duration, with each face being presented for 3.5 seconds separated by a 0.5 seconds inter-stimulus interval (ISI). There were 12.5 seconds long baseline periods between blocks during which participants were instructed to fixate on a cross in the centre of the screen. The dichotomized choices 'not approachable' and 'very approachable' were shown on the screen. Participants had to press one of two buttons to indicate their response.

**Figure 4.2.1: Images Shown in Scanner (Approachability Task)**

Three examples of non famous faces used for making approachability and gender judgements, followed by a diagram of baseline block (fixation cross). In approachability blocks 6 faces were shown (for 3.5 seconds each, in a random order with a 0.5s inter stimulus interval) and participants were asked to indicate one of the choices 'approachable' or 'not approachable' shown on the screen below the image. The same face was shown in the gender condition, where the participants were asked to indicate the gender of the face. The approachability minus gender contrast, which is considered here, therefore represents the neural response to explicitly processing the information in the face and making an approachability decision.

| Group | Number | Age (SD) | NART (SD) | Males (Females) | Right Handed (Left) |
|---|---|---|---|---|---|
| **Patients** | 20 | 37.5 (8.2) | 111.6 (9.8) | 12 (8) | 15 (5) |
| **Controls** | 24 | 35.13 (9.7) | 114.6 (6.5) | 16 (8) | 24 (0) |

**Table 4.2.1 Demographics for Patients and Controls (Approachability Task)**

This table shows the demographic details of all the participants included in this analysis including the individuals with schizophrenia (patients) and the healthy control participants (controls). There were no significant differences (see section 4.3.1 for details)

### 4.2.3 Behaviour Evaluation within Scanner

Responses were scored against the rating for the picture which had been previously assigned as described above, with a maximum score of 36 in each category. Response times were recorded for all judgments made in the scanner. Task performance was controlled for using these measures.

### 4.2.4 Imaging

The fMRI image acquisition was performed as described in Chapter two.

### 4.2.5 Image analysis

The acquired images were analysed. Details are described in Chapter two.

### 4.2.6 Connectivity analysis

Connectivity analysis was performed using psycho-physiological interaction (PPI), as described in Chapter two.

## 4.3 Results

### 4.3.1 Demographics

There were no significant differences found between individuals with schizophrenia and healthy controls in age ($F_{1,42} = 0.1$, $p = 0.1$), National Adult Reading Test (NART) IQ ($F_{1,42} = 0.0$, $p = 0.9$) or gender (Fisher's Exact Test, $p = 1.0$).

### 4.3.2 Difference in Emotional Behaviour between Groups

Within scanner behaviour measures of approachability and gender discrimination showed no significant difference in making gender or approachability judgements between the groups. Further, both groups demonstrated a high degree of accuracy for both approachability (patients 80% correct, SD 13.1%, control participants 87% correct, SD 13.1%) and gender (patients 94% correct, SD 14%, control participants 95% correct, SD 13.7%).

### 4.3.3 Neural Response for Approachability Judgement in Health

While making approachability, compared to gender judgements, healthy participants significantly over-activated a large cluster with a peak in the left superior frontal gyrus extending over the medial frontal gyrus ($P_{corr} < 0.001$, $K_E = 2652$, T = 5.57, -8, 40, 52), a cluster with a peak in left fusiform gyrus, extending over the lingual and inferior occipital gyrus ($P_{corr} < 0.001$, $K_E = 1660$, T = 5.30, -28, -90, -34), a cluster with peak activation in the right inferior frontal gyrus ($P_{corr} = 0.007$, $K_E = 978$, T = 4.69, 56, 24, 0), a cluster with a peak in the right fusiform gyrus ($P_{corr} = 0.007$, $K_E = 994$, T = 4.27, 30, -88, -36) and a large cluster with peak in the left superior temporal

gyrus and extending over left inferior frontal gyrus ($P_{corr}$ = 0.001, $K_E$ = 1290, T = 4.55, -52, 18, -10) for the approachability versus gender contrast (thresholded at $p < 0.005$, uncorrected). There was also activation of the right amygdala ($P_{corr}$ = 0.029, $K_E$ = 23, T = 3.96, 18, 2, -18) and left amygdala ($P_{corr}$ = 0.035, $K_E$ = 17, T = 0.035, -22, -8, -20), which reached corrected significance with an amygdala SVC. See table 3 and figure 3 in the Appendix.

### 4.3.4 Increased Neural Response in Individuals with Schizophrenia

Compared to the healthy participants, individuals with schizophrenia over-activated a large cluster with peak in the right precuneus, extending over the right inferior and superior parietal gyrus, as well as the right supra marginal and right superior temporal gyrus ($P_{corr} < 0.001$, $K_E$ = 3152, T = 5.16, 16, -66, 44) and another cluster with peak in the inferior frontal gyrus and extending over the middle and superior frontal gyrus ($P_{corr} < 0.001$, $K_E$ = 1955, T = 4.69, 58, 24, 24). There were no significant activations in the reverse contrast and there was no significant difference in the amygdala, even using SVC. See table 4.3.1 and figure 4.3.1 below.

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| < 0.001 | 3152 | 5.16 | 16, -66, 44 | Precuneus |
| < 0.001 | 1955 | 4.69 | 58, 24, 24 | Inferior Frontal Gyrus |

**Table 4.3.1 Increased Activation in Patients**

This table shows the regions with significantly increased activation in patients, for the approachability versus gender contrast, thresholded at $p < 0.005$, uncorrected

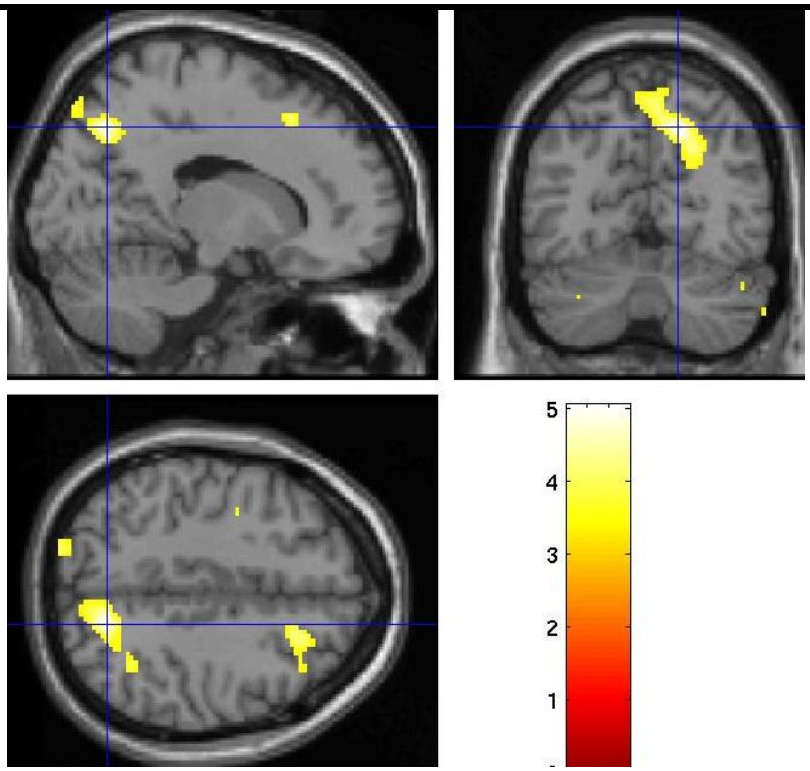



**Figure 4.3.1 Increased Activation in Patients**

This figure is a SPM illustrating the regions with significantly increased neural activation in patients with schizophrenia, compared to healthy controls, for the approachability versus gender contrast, in yellow, thresholded at $p < 0.005$, uncorrected. The cross hairs are at MNI coordinates 16, -66, 44

### 4.3.5 Amygdala Connectivity in Healthy Participants

From the left amygdala, healthy participants demonstrated significant effective connectivity to a cluster with peak in the left fusiform gyrus and extending over the cerebellum ($p_{corr} < 0.001$, $K_E = 1108$, T = 5.76, -36, -54, -14), and a cluster with peak in the right fusiform gyrus and extending over the cerebellum ($p_{corr} = 0.001$, $K_E = 887$, T = 4.62, 40, -56, -24). These are illustrated in table 3 and figure 3 in the appendix.

From the right amygdala, healthy participants showed significant effective connectivity to a large cluster with peak in the left fusiform gyrus, extending over the lingual gyrus, inferior occipital gyrus and cerebellum ($p_{corr} < 0.001$, $K_E = 1413$, T = 6.33, -16, -96, 0). They also showed significant effective connectivity from the right amygdala to a cluster in the middle and superior frontal gyrus ($p_{corr} = 0.046$, $K_E = 424$, T = 4.07, -16, 34, 52), and a large cluster with peak in the right inferior occipital, extending over the lingual gyrus, fusiform gyrus, cuneus and cerebellum ($p_{corr} < 0.001$, $K_E = 2250$, T = 6.11, 32, -46, -26). Further, from the right amygdala healthy controls also show a trend to significant connectivity to the left inferior frontal gyrus ($p_{corr} = 0.082$, $K_E = 368$, T = 5.05, -50 38 -14) as well as another cluster in the left middle frontal gyrus ($p_{corr} = 0.060$, $K_E = 398$, T = 4.18, -40 -18 68). These are illustrated in table 4 and figure 4 in the appendix.

### 4.3.6 Reduced Connectivity in Individuals with Schizophrenia

No brain regions were found to have significantly higher connectivity from the left or right amygdala for the patients, compared to control participants.

Individuals with schizophrenia showed significantly reduced effective connectivity from the left amygdala to a cluster in the right para-hippocampal gyrus ($P_{corr}$ = 0.042, $K_E$ = 508, peak T = 3.89, 20, -12, -24) and a cluster with peak in the right inferior frontal gyrus, extending over parts of the insula and thalamus (34, 0, -6, $P_{corr}$ = 0.004, $K_E$ = 802, peak T = 4.54), as shown in table 4.3.2 and figure 4.3.2 below.

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| 0.004 | 802 | 4.54 | 34, 0, -6 | Inferior Frontal Gyrus |
| 0.042 | 508 | 3.89 | 20, -12, -24 | Para-hippocampal Gyrus |

**Table 4.3.2 Reduced Connectivity in Patients, from Left Amygdala**

This table shows the regions with reduced effective connectivity in patients with schizophrenia, compared to healthy controls, for the approachability versus gender contrast, from the left amygdala, thresholded at $p < 0.005$, uncorrected.

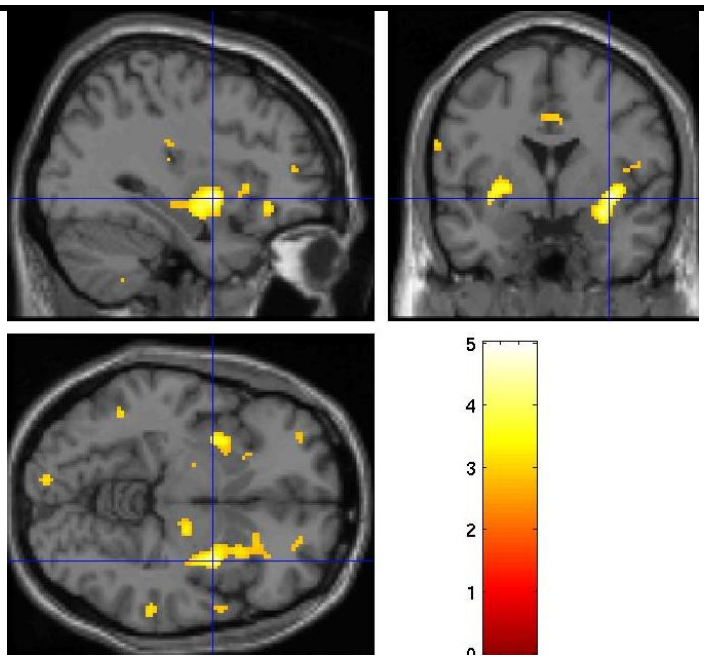



**Figure 4.3.2 Reduced Connectivity in Patients, from the Left Amygdala**

This figure is a SPM illustration the regions with reduced effective connectivity in patients with schizophrenia, compared to healthy controls, for the approachability versus gender contrast, from the left amygdala, in yellow, thresholded at $p < 0.005$, uncorrected. The cross hairs are at MNI coordinates 34, 0, -6.

Further, individuals with schizophrenia however showed significantly reduced connectivity from the right amygdala to a large cluster with peak activation in the claustrum ($P_{corr}$ = 0.002, $K_E$ = 958, T = 4.29, 34, 4, -10), also extending over the, right inferior frontal gyrus and parts of the insula and superior temporal gyrus, as shown in table 4.3.3 and figure 4.3.3 below.

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| 0.002 | 958 | 4.29 | 34, 4, -10 | Claustrum |

**Table 4.3.3 Reduced Connectivity in Patients, from the Right Amygdala**

This table shows the regions with reduced effective connectivity from the right amygdala in patients compared to controls, for approachability versus gender, thresholded at $p < 0.005$, uncorrected.

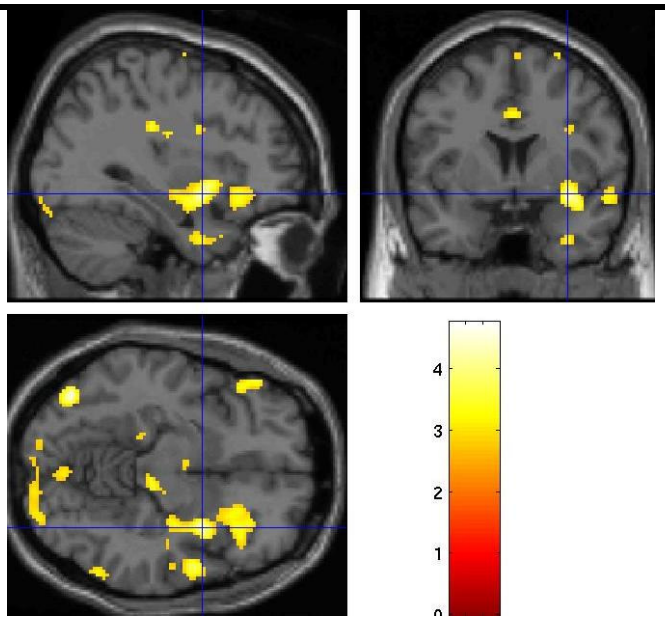



**Figure 4.3.3 Reduced Connectivity in Patients, from the Right Amygdala**

This figure is a SPM illustrating the regions with reduced effective connectivity in patients with schizophrenia, compared to healthy controls, for the approachability versus gender contrast, from the right amygdala, in yellow, at a threshold of $p < 0.005$, uncorrected. The cross hairs are at MNI coordinates 34, 4, -10.

### 4.3.7 Correlation of Connectivity with Behaviour and Traits

Correlation analysis was performed to assess whether connectivity calculated above was related to trait measures SQ and EQ (described in section 4.2.1 above). Further, correlation analysis was also performed to assess whether connectivity was related to measures of within scanner approachability and gender judgment performance or response times for all participants. None of these correlations were significant.

### 4.3.8 Correlation of Connectivity with Symptoms in Patients

Correlation analysis was performed to assess whether connectivity was related to the symptoms in patients. The PANSS total score, PANSS positive or PANSS negative symptoms were used for this analysis and no significant correlations were found.

On further exploratory testing of correlation with items, however, a trend to significant inverse correlation was found with the PANSS negative score for abstract thinking ($p = 0.054$, $r = -0.437$), as well as for Anxiety ($p = 0.078$, $r = 0.404$).

### 4.3.9 Correlation of Connectivity with Antipsychotic Dose

Correlation analysis was performed to assess whether connectivity calculated above was affected by antipsychotic medication dosage of chlorpromazine equivalents (Barr et al., 2010, Woods 2003). There were no significant correlations found.

## 4.4 Discussion

In the present study, healthy individuals recruited brain regions including the left superior and medial frontal gyrus, left lingual gyrus, left inferior occipital gyrus and left superior temporal gyrus as well as the bilateral fusiform gyrus, inferior frontal gyrus (IFG) and amygdala, while making approachability judgements from faces. Further, during approachability judgement, healthy individuals showed significant effective connectivity between both the right and left amygdala and the bilateral fusiform gyrus and cerebellum, as well as between the right amygdala and parts of the bilateral lingual gyrus and left superior frontal gyrus.

The brain regions recruited by the healthy individuals for making approachability judgements in the present study are consistent with regions linked to social function (Adolphs, 2001, Brothers, 1990), particularly for processing faces (Keuken 2011, Haxby et al., 2000), and making complex social judgements from faces (Winston et al., 2003, Willis et al., 2010, Saxe, 2006). The fusiform gyrus is strongly associated with face processing (Kanwisher et al. 1997) and the amygdala is a central hub in social and emotional function (Phelps and LeDoux, 2005, Amaral, 1992, Haxby et al., 2000). The medial prefrontal cortex has been associated with theory of mind processing (Gallagher et al., 2000, Amadio and Frith, 2006). The lingual, superior temporal and inferior occipital gyri have been associated with processing emotion (Fusar-Poli et al., 2009, Hoffman and Haxby 2000, Adolphs, 2001). The cerebellum has also been associated with high level social function (as reviewed in Schmahmann 2004). Therefore the results for the healthy individuals of

the present study are in line with the expected pattern of brain regions associated with social functioning.

Compared to healthy individuals, the individuals with schizophrenia were found to overactivate parts of the right precuneus, right inferior and superior parietal gyrus, the right supramarginal and right superior temporal gyrus. Further they also overactivated parts of the inferior frontal gyrus, the middle and superior frontal gyrus. Previous studies have shown that individuals with schizophrenia demonstrate an atypical set of brain regions during facial emotion processing. One study found that when comparing facial emotion versus identity matching, schizophrenia patients only activated the middle and inferior frontal gyri, the frontal operculi and the right insular cortex, whereas healthy controls as activated the fusiform and middle temporal gyri, left superior temporal gyrus, and right inferior and middle frontal gyrus (Quintana et al., 2010). Many of the regions which are believed to play a central role in processing facial emotion processing, such as the amygdala, the medial pre-frontal cortex have been shown to be affected in schizophrenia (for review see Pinkham et al., 2003). Further, it has been suggested that the recruitment of non task related areas seen in patients with schizophrenia represent a compensatory mechanism for dysfunction within the normal task networks (Wolf et al., 2007, Kim et al., 2010).

Further, patients with schizophrenia were found in the present study to show reduced effective connectivity between the amygdala and right para-hippocampal gyrus (PHG), right precuneus and right IFG. These are important brain regions for making high level social judgements. The amygdala is instrumental in processing the

emotional aspects of stimulus, especially related to threat (Phelps and LeDoux, 2005), the PHG has been associated with emotional processing (Murty et al., 2011, Fanselow & LeDoux, 1999, Yaniv et al., 2000), the precuneus is associated with self related processing, or taking a first person perspective (Cavanna and Trimble, 2006) as well as mentalizing and theory of mind (Mar, 2011, Fletcher at al., 1995b), in addition to being associated with empathy and the mirror neuron system (Keuken et al., 2011, Ramsey and Hamilton, 2010), the IFG is associated with an inhibitory role in making decisions related to risk (Knoch et al., 2006). Activity in this region has been shown to correlate with personality differences in risk aversion (Christopoulos, et al., 2010). Therefore it might be that the increased IFG activity, as well as reduced connectivity between the IFG and amygdala in individuals with schizophrenia reflects increased sense of threat to themselves while assessing approachability in faces of others. This would also explain many symptoms of the disorder which relate to inappropriate social behaviour and inappropriate sense of risk. These brain regions are also known to be abnormally activated during social cognition in schizophrenia (Li et al., 2010, Habel et al., 2010, Hall et al., 2004, Lepage et al., 2011, Kumari et al., 2010, Rylands et al., 2011). Fronto-temporal connectivity for social cognition between regions including the ones indicated in the present study has been shown, and failure of top-down cognitive regulatory influence on affective functions, has been implicated in schizophrenia (White et al., 2010, Lee et al., 2004). Additionally, white matter abnormalities have been reported in some of these regions including the superior and middle frontal gyrus as well as middle temporal gyrus, and the precuneus in schizophrenia (Antonius et al., 2011). Interestingly in the context of

disconnection, both the amygdala and the precuneus are known to be major connectivity hubs in the brain (Tomasi et al., 2011, Phelps and LeDoux, 2005).

Together this converging evidence supports the finding of abnormalities in the neural mechanism for judging approachability in schizophrenia contributing to the social behaviour impact seen in the disorder, and the current evidence supports this disconnection model of social deficits in schizophrenia.

A limitation of the present study is that I have examined effective connectivity, but not investigated any related structural connectivity or other underlying causal factors, which could be addressed in future work. Further, although PPI estimates effective connectivity from a source to target regions, it does not indicate a causal nature of the influence (Friston et al., 1997). Finally, there might be a possible influence of antipsychotic medication in patients on synaptic plasticity (Stephan et al., 2001), although no evidence was found of a correlation of medication dose with effective connectivity.

In conclusion the results of the present study demonstrates for the first time that individuals with schizophrenia show abnormal activation and effective connectivity in key parts of the social brain while judging approachability, which might be an important cause of the social behaviour deficits seen in schizophrenia.

# CHAPTER FIVE:

# Effect of Variation in BDNF on Fear Processing

## 5.1 Introduction

In this chapter I have examined the impact of variation in the brain derived neurotropic factor (BDNF) gene, a risk gene for schizophrenia on effective connectivity for fearful face in healthy individuals. These results have been published as Mukherjee et al., 2010.

BDNF is a neurotrophin growth factor involved in dendritic trafficking, synaptic localization and affects dendritic spines (Ji et al., 2005), and thereby synaptic plasticity and long term potentiation (LTP) (Lu, 2003, Poo, 2001), particularly in the hippocampus (Lu and Gottschalk, 2000) as well as the insula (Escobar, 2003) and anterior cingulate cortex (ACC) (Lang et al., 2007, Takahashi, 2000). BDNF is important for fear related learning (Hall et al., 2000; Rattiner et al., 2005), and BDNF deletion in the hippocampus effects aversive memory (Heldt et al., 2007).

A functional polymorphism, val66met (rs6265), has been identified in the human BDNF gene, and in-vitro studies have shown that substitution of the met allele in this single nucleotide polymorphism (SNP) diminishes activity-dependent secretion of BDNF (Egan et al., 2003; Chen et al., 2006). Carriers of the met allele showed structural abnormalities in regions including the insula (Nemoto et al., 2006) and hippocampus (Bueller et al., 2006; Frodl et al., 2007; Montag et al., 2009) and ACC (Gallinat et al., 2010). Functional imaging studies showed that met allele carriers overactivated the hippocampus in various episodic memory tasks (Egan et al., 2003; Hariri et al., 2003; Chen et al., 2006) and behavioral studies have shown

met allele carriers to have impaired associative learning of aversive cues (Hajcak et al., 2009).

These findings about the val66met SNP have led to examination of its connection with affective psychopathology (Hashimoto et al., 2004; Hashimoto 2007; Gatt et al., 2009). However, these have not led to a clear consensus, as reviewed by Groves et al., 2007 and Martinowich, Manji and Lu 2007. This heterogeneity of results might be due to several factors. These affective disorders tend to have a clinically complex nature (Jiang et al., 2005; Lang et al., 2005) and polygenic aetiology (Lang et al., 2005). Interaction between BDNF and other genes (Pezawas et al., 2008), environmental factors (Casey et al., 2009), or between functional variants of BDNF (Jiang et al., 2005) might further complicate the relation between this SNP and psychopathology. Finally, BDNF is an extremely complex gene in humans and it shows differential expression-based factors including context, brain region and developmental stage (Martinowich Manji and Lu, 2007). Therefore it has been suggested that studying the effect of the BDNF gene on common behavioural traits or emotional attributes may help elucidate how the val66met polymorphism affects psycho-pathology (Liu et al., 2004; Gottesman and Hanson 2005; Monfils, Cowansage et al., 2007; Hajcak et al., 2009). Fear processing, associated commonly with symptoms found in multiple psychiatric disorders (Monfils et al., 2007), is a candidate attribute. Previous imaging studies have found neural overactivation in response to an emotional stimulus in met allele carriers (Montag et al., 2008; Lau et al., 2010) using functional imaging. However, genetic variation in BDNF may also affect functional connectivity as BDNF impacts upon the regulation of synaptic plasticity (Poo 2001, Lu 2003, Lu and Chow 1999,

Patterson et al., 2001, Pang et al., 2004), which in turn is one of the main factors associated with functional connectivity (Friston 1998, Stephan et al., 2009). Therefore, examining connectivity for fear processing might further elucidate the effects of the met allele on affect processing BDNF. Therefore in the present study I examine the neural reaction and connectivity to fear stimuli in humans using fMRI.

## 5.2. MATERIALS AND METHODS

This section describes the methods for the analysis of effects of the BDNF val66met polymorphism on the neural response to fear processing. Much of the procedure is uniform for each individual analysis. The common methods (5.2.1 - 5.2.4) have been described in detail in chapter 2, but are briefly repeated here for completeness.

### 5.2.1 Participants

Only healthy subjects were used in this analysis, to avoid medication confounds and due to smaller study numbers in patient group. Of the 51 overall healthy subjects recruited for the study (see Chapter two), 42 subjects were included in this analysis, as the remaining subjects has to excluded for factors including lack of active participation as identified during scanning, consent to use blood sample and ethnicity. The demographics for all the subjects are shown in Table 5.2.1 below. All participants were Caucasian right handed and had no personal or family history of psychiatric or neurological conditions, nor any factors precluding MRI examination. Participants were split into two groups according to genotype; val homozygotes, n = 26, and carriers of one or more met allele, n = 14. Met allele carriers were grouped together due to the relatively low population frequency (n = 4 in this cohort) of met homozygotes (Hariri et al., 2003). Genotypes were in Hardy-Weinberg Equilibrium ($Chi^2 = 3.21$, n.s). All participants gave written informed consent to take part in the study, and appropriate ethics clearance was obtained.

| Group | Number | Age (SD) | NART (SD) | Males (Females) | Right Handed (Left) |
|---|---|---|---|---|---|
| **Val Homozygotes** | 26 | 32.27 (8.2) | 116.5 (7.1) | 14 (12) | 25 (1) |
| **Met Carriers** | 14 | 28.6 (5.1) | 116.5 (6.7) | 7 (7) | 14 (0) |

**Table 5.2.1 Demographic Details of all Participants**
This table shows the demographic details of all the participants included in this analysis.

### 5.2.2 Genotype Analysis

Genotype at SNP rs6265 was determined for each included participant, using genomic DNA isolated from a venous blood sample. The genotyping used standard TaqMan assays, by the TaqMan polymerase chain reaction (PCR) based method (TaqMan, AssayByDesign, Applied Biosystems, Foster City, California). The Assay ID for the genotyping was C__11592758_10 and the context sequence is TCCTCATCCAACAGCTCTTCTATCA[C/T]GTGTTCGAAAGTGTCAGCCAAT GAT. This testing was conducted at the Wellcome Trust Clinical Research Facility, Edinburgh, United Kingdom (www.wtcrf.ed.ac.uk).

### 5.2.3 Behavioural Testing Outside the Scanner

Following the scanning sessions, a standardized test of facial emotion recognition was conducted (Young, 2002). Facial images for ten people, taken from the Ekman and Friesen series (Ekman and Friesen, 1976), were used in this test. For each face, images corresponding to six basic emotions: happiness, surprise, fear, sadness, disgust, and anger (giving a total of 60 images, 10 for each emotion) were shown in randomized 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. Participants were asked if they understood the meanings of the emotional names. If not, brief standardized descriptions were given. Following this, computer generated images morphed between emotions likely to be confused were used to test of emotion recognition further (Sprengelmeyer et al., 1996, Young 2002). The names of the six emotions were displayed and participants were required to choose the appropriate responses by clicking the computer mouse. Additionally, standard tests for facial identity recognition were conducted using the 'Benton Test of Facial Recognition' (Benton et al., 1983). There was no time limit for responding. The next image was not shown until the subject had made a response. No feedback was given as to the appropriateness of any responses.

### 5.2.4 Experimental Design

The imaging was performed using a block-design experiment, with three conditions: fear, neutral and baseline. During the fear blocks six faces from the Ekman and Friesen series (Ekman and Friesen 1976) with a fearful emotional expression were presented for 3.5 seconds each, in a random order with a 0.5s inter-stimulus interval, and during the neutral blocks the same six faces showing a neutral emotional expression were presented similarly. During baseline blocks participants were instructed to look at a fixation cross for 12.5 seconds. Fear and neutral blocks were alternated, each being presented three times, with the starting order counterbalanced across participants, and seven interleaved baseline blocks were shown with these. For both the fear and neutral conditions participants were required to select the gender of the facial image. Response time as well as within scanner behavioural measures

where recorded (number of correct gender identifications made). These were used to control for non-participation in the task.

### 5.2.5 Imaging

The fMRI image acquisition was performed as described in Chapter two.

### 5.2.6 Image Analysis

The acquired images were analysed The fMRI image acquisition was performed as described in Chapter two.

### 5.2.7 Connectivity Analysis

Connectivity analysis was performed using psycho-physiological interaction (PPI), as described in Chapter two.

## 5.3. Results

### 5.3.1 Demographics

Met carriers did not differ from the val homozygotes for any of the demographic measures, as summarized in Table 5.2.1 (Age: F1,38 = 2.37, P = 0.132, IQ as measured by the National Adult Reading Test (NART IQ) (Nelson and Willison 1991): F1,38 = 0.00, P = 0.986, Gender: F1,38 = 0.05, P = 0.822).

### 5.3.2 Effect of Genotype on Neural Response

All subjects were found to have performed the task in the scanner, and together demonstrated significant left amygdala activation for the fear versus neutral contrast, consistent with previous functional imaging studies using similar tasks (Hall et al., 2008; Montag et al., 2008; Lau et al., 2010). Comparing brain activation between val homozygotes and met allele carriers for the fear versus neutral contrast (thresholded at $p < 0.005$, uncorrected), no significant differences were found in the amygdala bilaterally using a bilateral amygdala SVC.

Met allele carriers were found, however, to significantly overactivate a cluster covering parts of the ACC and extending over parts of the prefrontal cortex ($p_{corr} < 0.001$, $K_E = 1913$, Peak T = 5.41, coordinates = 0, 14, 52), a region extending over parts of the brain stem and cerebellum ($p_{corr} = 0.034$, $K_E = 544$, Peak T = 5.34, coordinates = 18, -12, -36), a cluster extending over parts of the left insula ($p_{corr} < 0.001$, $K_E = 1625$, Peak T = 5.26, coordinates = -32, 42, -2), and another over parts of the right insula ($p_{corr} = 0.005$, $K_E = 790$, Peak T = 3.82, coordinates = 50, 10, 4), see

Figure 5.3.1, Table 5.3.1 below. No brain regions were significantly more activated by the val homozygotes than by met allele carriers.

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| p < 0.001 | 1913 | 5.41 | 0 14 52 | Midline Anterior Cingulate Cortex |
| p < 0.001 | 1625 | 5.26 | -32 42 -2 | Left Insula |
| 0.005 | 790 | 3.82 | 50, 10, 4 | Right Insula |
| 0.034 | 544 | 5.34 | 18 -12 -36 | Right Brain Stem |

**Table 5.3.1 Regions Showing Increased Activation in Met Carriers**

This table shows the regions with significantly increased activation in met carriers, compared to val homozygotes, for the fear versus neutral contrast, thresholded at p < 0.005, uncorrected.

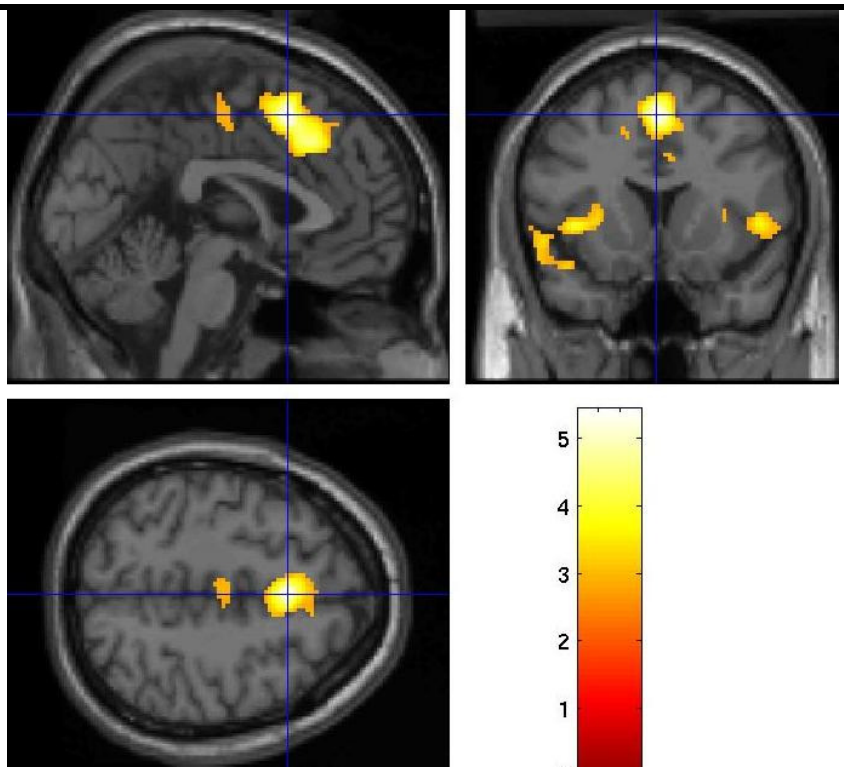



**Figure 5.3.1 Regions Showing Increased Activation in Met Carriers**

This figure is a SPM illustrating the regions with increased neural activation in met allele carriers as compared to the val homozygotes (val-val < val-met + met-met), for the fear versus neutral contrast, The figure is a statistical parametric map (SPM) with regions with significantly decreased activation shown in yellow, thresholded at p < 0.005, uncorrected. Extent threshold 500 voxels. The cross hairs are at MNI coordinates 0, 14, 52

### 5.3.3 Effect of Genotype on Effective Connectivity

Connectivity analysis performed using the anatomically derived bilateral amygdala seeds showed no significant differences in connectivity between the met allele carriers and val homozygotes.

Subsequently connectivity analysis was performed once for each of the clusters over-activated by the met allele carriers as seed VOI. From the VOI in the ACC (for the cluster extending over the medial ACC with peak MNI coordinates 0, 14, 52), I found that (at threshold 0.005 uncorrected) the carriers of the met allele showed significantly decreased effective connectivity corresponding to the fear versus neutral contrast, to a large cluster in the hippocampus and para-hippocampal gyrus ($p_{corr}$ = 0.012, $K_E$ = 690, Peak T = 4.28, coordinates = -22, -18, -6), see Figure 5.3.2, Table 5.3.2.

Further, met allele carriers also showed significantly reduced effective connectivity from the VOI in the left and right insula corresponding to the fear versus neutral contrast (at threshold 0.005 uncorrected) to regions in the cerebellum ($p_{corr}$ = 0.005, $K_E$ = 837, Peak T = 4.16, coordinates = 4, -48, -46, and $p_{corr}$ = 0.003, $K_E$ = 806, Peak T = 4.65, coordinates = -8, -46, -42, respectively).

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| < 0.001 | 1511 | 7.73 | 50, -48, 52 | Temporo-Parietal Junction (TPJ) |

**Table 5.3.2 Reduced Connectivity in Met Carriers**

This table shows the regions with significantly lower effective connectivity from the anterior cingulate cortex, corresponding to the fear versus neutral contrast, at threshold 0.005, uncorrected, in met allele carriers (val-met + met-met), as compared to the val homozygotes (val-val).

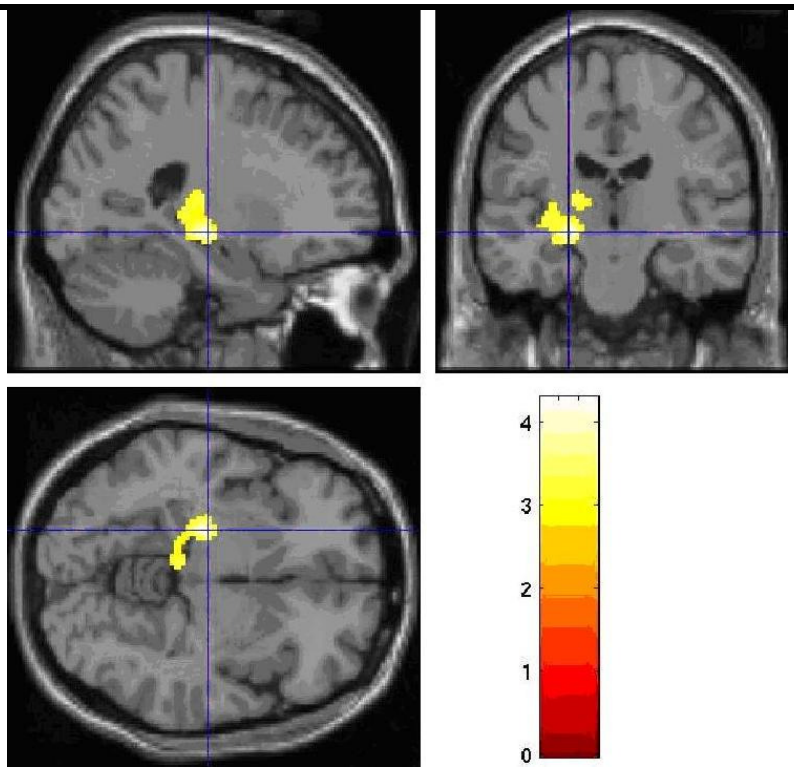



**Figure 5.3.2 Reduced Connectivity in Met Carriers**

This figure is a SPM illustrating regions with significantly lower effective connectivity from the anterior cingulate cortex, corresponding to the fear versus neutral contrast, at threshold 0.005, uncorrected, in met allele carriers (val-met + met-met), as compared to the val homozygotes (val-val). Regions with significantly decreased connectivity are in yellow. Extent threshold 400 voxels. Cross hairs at 50, -48, 52. This map shows a cluster extending over parts of the hippocampus and para-hippocampal gyrus.

### 5.3.4 Effect of Genotype on Emotional Behaviour

When comparing the ability to correctly identify the emotion in faces between val homozygotes and met allele carriers, performance was not found to be significantly different for any of the emotions except for a trend to a significant difference for the emotion of fear ($F_{1, 38} = 2.78$, $p = 0.104$). However, covarying for age and NART IQ, both of which were found to independently influence fear recognition performance (fear with NART IQ: $r = 0.52$, $p = 0.001$, and fear with age: $r = -0.37$, $p = 0.018$), revealed that the ability to correctly identify the facial expression of fear was significantly impaired in met allele carriers ($F_{1, 36} = 9.00$, $p = 0.005$), as shown in Figure 5.3.3.

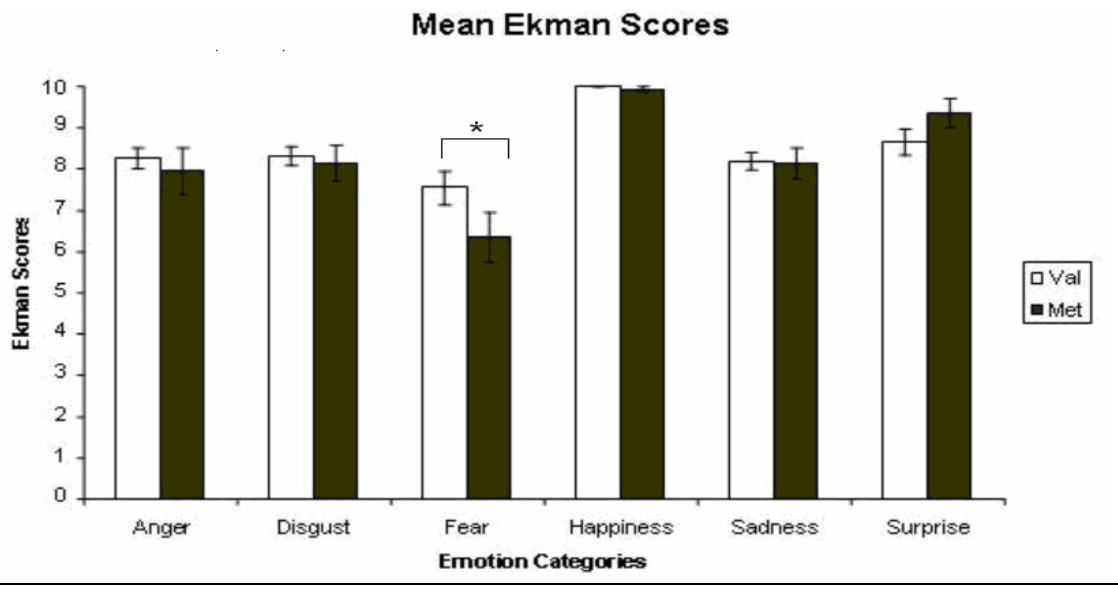



**Figure 5.3.3 Results of Behaviour Testing Outside the Scanner**

This figure shows the results of the behaviour testing conducted outside the scanner for all the participants. This testing was conducted using Ekman faces for the six basic emotions Anger, Disgust, Fear, Happiness, Sadness and Surprise. The details of the analysis are described above. Facial emotion recognition in met carriers and val homozygotes: Ekman facial emotion recognition scores were found to be significantly lower in met allele carriers, only for the fear ($F1,36 = 9.00$, $P = 0.005$), when covarying for Age & IQ as measured by National Adult Reading Test (NART IQ).

### 5.3.5 Post-Hoc Examination of Met Homozygotes

Motivated by multiple previous studies which implicated a gene dose effect in their finding associated with BDNF (Egan et al., 2003; Chen et al., 2006; Montag et al., 2008), I performed a post-hoc analysis of the met homozygotes separately. Despite the small number of met homozygotes (Table 5.2.1) this analysis indicated a possible dose response relationship with met allele load, or an additive genetic model (Table 5.3.3, Figure 5.3.4). Comparing brain activation between val homozygotes and met homozygotes for the fear versus neutral contrast at thresholded at $p < 0.001$, met homozygotes showed significant overactivation which matched the overactivation shown by all met allele carriers at thresholded at $p < 0.005$ (Figure 5.3.4). Comparing the Ekman fear scores in the post scan behavioural analysis, which were found significantly deficient in met allele carriers as compared to val homozygotes when covarying for age and NART IQ this effect was seen to be especially pronounced in met homozygotes. A significant difference was found between the three groups ($F_{2, 35} = 4.83$, $p = 0.014$). Notably, the mean fear scores were found to be 7.54 (SD 2.06) for the val homozygotes, 6.90 (SD 2.28) for the val-met heterozygotes, and 5.00 (SD 1.83) for the met homozygotes (Figure 5.3.5).

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| p < 0.001 | 1805 | 5.20 | -32, 42, 0 | Left Insula |
| p < 0.001 | 1976 | 5.09 | 0, 14, 50 | Medial Anterior Cingulate Cortex |
| p < 0.001 | 1724 | 4.58 | 54, 18, -2 | Right Insula |

**Table 5.3.3 Post-Hoc Analysis of Over-Activation in Met Homozygotes**

This table shows the brain regions showing significantly increased activation in the met homozygotes, compared to the val homozygotes, at threshold $p < 0.005$, uncorrected, for the fear versus neutral contrast. The table shows the $P_{corr}$ as the whole brain corrected significance, $K_E$ as the extent, Peak $T$ as the peak t value, the peak coordinates, in the Montreal Neurological Institute (MNI) coordinates

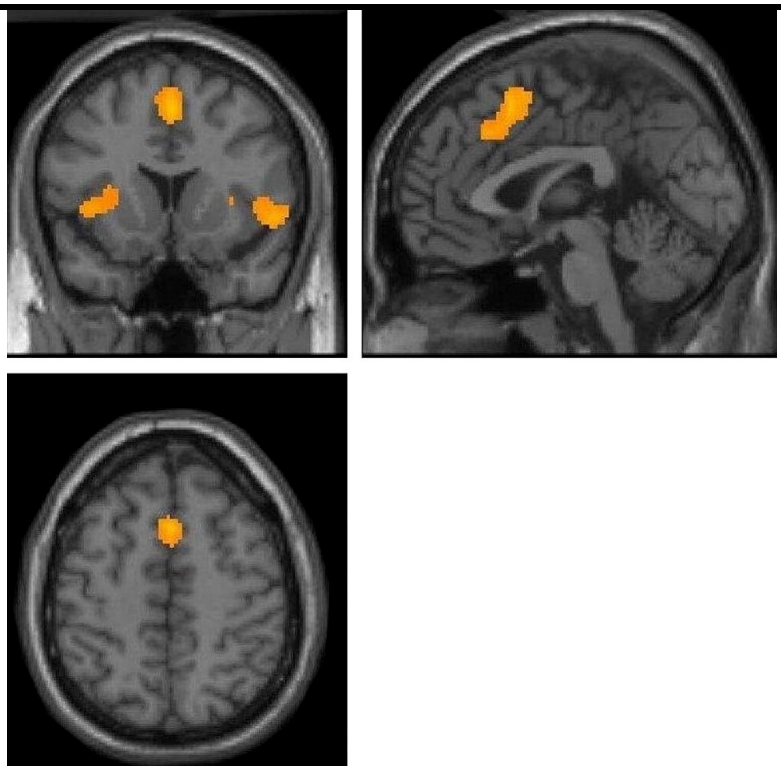


**Figure 5.3.4 Post-Hoc Analysis of Over-Activation in Met Homozygotes**

.Results of post-hoc analysis in met homozygotes, motivated by past studies showing gene dose effect. A shows increased activation in met homozygotes. The regions in orange represent the significant group differences found at a threshold of $p < 0.005$ (whole brain, corrected). Extent threshold 500 voxels. This map shows clusters extending over parts of the ACC and bilateral insula

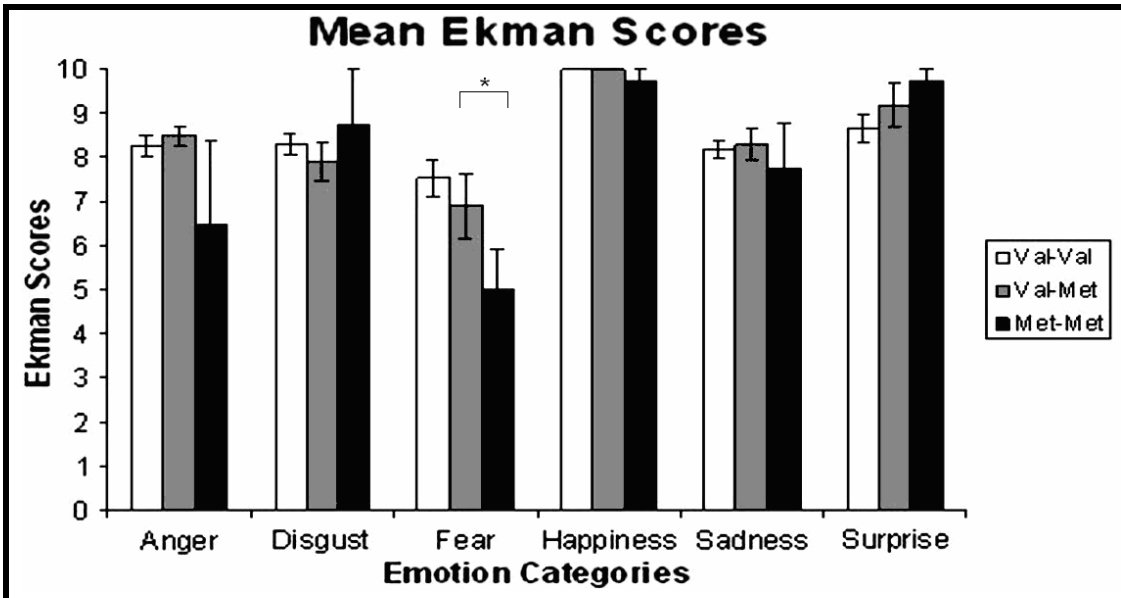



**Figure 5.3.5 Post-Hoc Analysis Behaviour of Met Homozygotes**

This figure shows the facial emotion recognition in met homozygotes, heterozygotes and val homozygotes, implicating a gene dose effect in the results.

## 5.4. Discussion

The BDNF val66met polymorphism has been associated with various psychiatric disorders (Hashimoto et al., 2004; Martinowich et al., 2007; Verhagen et al., 2008; Baig et al., 2010). However, only few previous studies have examined its effect on emotion processing in humans using brain imaging (Montag et al., 2008; Lau et al., 2010).

The results of the present study showed that in response to fearful faces, while all the subjects taken together showed neural activation in the amygdala, met allele carriers compared to val homozygotes overactivate regions including the ACC, bilateral insula and parts of the brainstem and cerebellum. Comparing connectivity from the ACC to the whole brain corresponding to the fear and neutral contrast, the met allele carriers showed significantly reduced effective connectivity to a cluster in the hippocampus and para-hippocampal gyrus. Met allele carriers also showed significantly impaired fear recognition in post-scan behavioral testing.

The brain regions overactivated by the met allele carriers have also been associated with regulation of the autonomic nervous system (Critchley 2009), and previous studies have also shown that BDNF val66met SNP can influence autonomic responses including responses to emotional stimuli (Gatt et al., 2009). Additionally, the ACC is associated with cognitive control of emotions (Allman et al., 2001), and abnormalities have been found in the ACC for the BDNF val66met SNP (Gallinat et al., 2010). Therefore, our results, along with these previous studies, suggest that met allele carrier's might be hyper-activating the autonomic response brain network in response to fear cues.

Furthermore, genetic variation in BDNF has been extensively associated with structural and functional abnormalities in the hippocampus (Patterson 1992; Egan et al., 2003; Bueller et al., 2006; Montag et al., 2009), particularly with respect to emotional and contextual memory (Korte et al., 1998; Hall et al., 2000; Heldt et al., 2007; Lau et al., 2010). Additionally, BDNF has been linked to synaptic plasticity (Lu and Gottschalk 2000; Lu 2003), one of the components of functional connectivity (Friston 1998). Therefore the decreased effective connectivity between the ACC and hippocampus found in the present study might suggest abnormal interaction between the brain emotion generation and regulation brain system with brain systems for storage of episodic memory.

The experimental task in the present study involves the emotion of fear, which has been strongly associated with the amygdala and abnormalities in this region have been reported for the BDNF met allele carriers (Montag et al., 2008; Montag et al., 2009; Lau et al., 2010). Interestingly however in this study I did not find any differential amygdala activation. This could be partly due to the nature of the stimuli used, as facial expressions denoting emotion are a crucial social cue and hence extremely well learned stimuli in human adults. The previous studies which reported differential amygdala activation based on the BDNF val66met SNP involved learning of new fear related associations, for example in the startle response paradigm, or explicit processing of fearful feelings on faces including those of unfamiliar actors (Montag et al., 2008; Lau et al., 2010). This kind of associative learning is what has been most strongly associated with the amygdala, (LeDoux 2003; Phelps and LeDoux 2005; Sigurdsson et al., 2007), especially in connection to BDNF (Rattiner et al., 2004; Rattiner et al., 2005; Chhatwal et al., 2006; Jones et al.,

2007; Monfils et al., 2007; Ou and Gean 2007; Yee et al., 2007). In contrast the present study evokes retrieval of previously learned fear-related emotional information, rather than involving the learning of novel fear associations. This is further supported by the differential connectivity between the medial temporal lobe, which is commonly associated with emotion related processing, and the ACC, found in this study. This suggests that the differential activation reported here in the ACC and insular regions are possibly related to retrieval of previously learned information, in order to make a decision about whether presented facial image is fearful, in the present study. Therefore taken together, this suggests that carrying the BDNF met allele impacts affective neural function, particularly impacting retrieval of previously stored knowledge about emotional stimulus which is used to process the current emotional context and respond to it. This neural effect might mediate the effects of this SNP seen in affective psychiatric disorders, especially those related to fear (Hashimoto et al., 2004; Martinowich et al., 2007). These effects on fear processing may provide a neural substrate for the effects of genetic variation in BDNF on susceptibility to psychiatric disorders, including schizophrenia and affective disorders.

Met homozygotes are rare amongst humans (2–3%) (Shimizu et al., 2004), and consequently have not been studied extensively. However, the studies which have examined met homozygotes of the BDNF gene implicated a dose response relationship with met allele load. In a previous study, Egan et al., found significantly diminished episodic memory in met homozygotes, and found a trend for the heterozygous met allele carriers. Additionally in the same study, neuronal integrity and synaptic abundance in the 'hippocampal formation', estimated *in-vivo* by

measuring N-acetyl-aspartate was found to be reduced in met allele carriers, and this impairment was more pronounced in met homozygotes (Egan et al., 2003). In an animal study of anxiety using BDNF transgenic mice, the phenotype of increased anxiety was found only in met homozygous mice (Chen et al., 2006), whereas all other traits found in previous human studies of the met allele were found to be replicated in all met allele carrying mice. Furthermore, a gene association study of anxiety by (Montag et al., 2008), found higher self reported trait anxiety in met allele carriers, with a more pronounced effect in met homozygotes. In the present study, the number of met homozygotes are too small to draw any definite conclusions. However the enhanced effect in the four met homozygotes does correspond with the earlier findings about this genotype mentioned above.

The findings in the present study are statistically robust, but the relatively small population size in the present study could be a limitation. Future work might address this by examining similar effects in larger populations, especially in met homozygotes, and also by taking into account other factors including state and trait anxiety measures. We do not have enough, however, to examine gene by group contrasts in the current dataset, therefore in this study the variation of effective connectivity with the BDNF gene in patients could not be investigated. This could be addressed in future work.

In conclusion, this study found that the met allele carriers of the BDNF val66met polymorphism over-activate a network of brain regions including parts of the ACC, bilateral insula and parts of the cerebellum and brainstem (brain regions which have previously been associated with regulation of the autonomic response system). They also show increased ACC connections with the hippocampus, a brain

region associated with memory, in response to fear stimuli, and show an impaired ability to recognize fear in facial images. These results provide convergent evidence indicating an effect of the val66met polymorphism on negative emotion processing, in keeping with previous genetic and animal studies.

# CHAPTER SIX:

# Effect of Variation in BDNF on Approachability Judgement

## 6.1 Introduction

In this chapter I have examined the impact of variation in the brain derived neurotropic factor (BDNF) gene, a risk gene for schizophrenia, on neural activation and effective connectivity for approachability judgement.

Schizophrenia is believed to have a polygenic aetiology and complex interactions between multiple genes and environmental factors determine disease manifestation. Therefore it has been suggested that investigating the effect of individual genes, such as BDNF, on brain functions commonly disrupted in schizophrenia may help elucidate how these genes interact with psychopathology, as discussed in chapter five.

As described in chapter four, social behaviour is commonly affected in schizophrenia, and a key aspect of social behaviour is making socially relevant judgements from faces. A distributed network of regions has been demonstrated to underlie this brain function, and therefore the degree of interactions within these brain networks is likely to be critical. Altered connectivity is therefore believed to be a core aspect of the pathology of schizophrenia, according to the disconnection hypothesis. Further, the results presented in chapter four supported this theory by demonstrating disconnection for social judgement in individuals with schizophrenia.

Synaptic plasticity, one of the main factors mediating connectivity, has been shown to be impacted upon by activity dependant secretion of BDNF, as discussed in detail in chapter five. Carrying the met allele in the val66met SNP of the BDNF gene has been linked to reduced activity dependant secretion of BDNF, therefore the

val66met SNP is likely to impact upon connectivity. This hypothesis was confirmed in chapter five for fear processing, a commonly altered trait in schizophrenia. Here, I extend this by investigating the effect of variation in the val66met SNP on connectivity for social judgment.

As described in chapter five, studying the effect of genes in patients is sometimes confounded by factors such as medication, disease duration and age of onset which have been shown to interact with BDNF, and further, complex interactions between several genes and environmental factors further complicate such investigation. Therefore it has been suggested that the interaction between BDNF and schizophrenia might be elucidated by examining how variation in the gene amongst healthy controls impacts brain functions known to be compromised in patients (Gottesman et al., 2005, Casey et al., 2010). Here I have investigated the effect of BDNF variation amongst healthy controls, for a brain function for which I have already found connectivity deficits in schizophrenia, as described in chapter four.

Environmental factors are believed to play an important role in determining manifestation of disorder in those with genetic vulnerability, and stress, particularly social and emotional, is a key environmental factor implicated in gene-environment models (Lawrie et al., 2008, Palomo et al., 2004, Howes et al., 2004, Benes et al., 1997). The social environment of an individual has been shown to impact upon manifestation and outcome of schizophrenia (Murphy and Raman, 1971). Interestingly, BDNF has also been related to the pathophysiology of stress (Colzato et al., 2011, Saruta et al., 2010) and BDNF levels are known to reduce under stress

(Fuchikami et al., 2010), particularly in the hippocampus (Duman and Monteggia, 2006, Vaidya and Duman, 2001).

Therefore understanding how the BDNF val66met SNP affects connectivity for a social task amongst healthy individuals might be valuable in further understanding how this SNP impacts social behaviour, in concert with with environmental factors such as stress to affect schizophrenia.

Early social experience, particularly social defeat, has been shown to affect long term activity dependant secretion of BDNF, and therefore synaptic plasticity (Branchi et al., 2009). Further, studies have demonstrated that this effect correlates with complex social behaviours later in life (Tsankova et al., 2006). In animals, BDNF has been shown to be critical for social learning, such as learning appropriate wariness of strangers after aversive social encounters (Berton and Nestler, 2005). BDNF deleted mice were found to have impacted long term learning and plasticity and failed to learn an appropriate aversion to social contact in response to aversive social experiences (Berton et al., 2006). These findings in animal models, have also been extended to humans to show reduced BDNF levels in situations of psycho-social stress (Castren et al., 2007, Hadjiconstantinou et al., 2001). Therefore BDNF appears to be important for learning from aversive social experiences and coping mechanisms in response to social stress. Such social learning from past experiences would be likely to critically impact future social behaviour, such as approachability judgement.

As described in the introduction, the amygdala is believed to play a key role in the network underlying social behaviour, and structural as well as functional,

abnormalities in the amygdala have been repeatedly shown in schizophrenia. Individuals with bilateral amygdala damage demonstrated deficits in wariness of unfamiliar people (Adolphs et al., 1998). Further, reduced volume of the amygdala and elevated emotional activation were demonstrated in individuals carrying the met allele of the BDNF val66met SNP, as described in chapter five. Therefore in this study, I have chosen to examine connectivity from the bilateral amygdala to the whole brain.

I hypothesize that effective connectivity for making approachability decisions from faces, from the amygdala, is significantly affected by variation in the BDNF val66met polymorphism. I suggest that this might mediate the effect of this gene on psychiatric disorders such as schizophrenia.

## 6.2. MATERIALS AND METHODS

This section describes the methods for the analysis of effects of the BDNF val66met polymorphism on neural processing for social cognition. Much of the procedure is uniform for each individual analysis. The common methods (6.2.1 - 6.2.4) have been described in detail in chapter 2, but are briefly repeated here for completeness.

### 6.2.1 Participants

Only healthy participants were used for this analysis, to avoid medication confounds and due to smaller study numbers in patient group. Of the 51 recruited healthy subjects, 42 subjects were included, remaining being excluded for factors including consent to use blood sample and ethnicity. The demographics for all the subjects are shown in Table 6.2.1. All participants were Caucasian right handed and had no personal or family history of psychiatric or neurological conditions, nor any factors precluding MRI examination. Participants were split into two groups according to genotype, val homozygotes, n = 28, and carriers of one or more met allele, n = 14. Met allele carriers were grouped together due to the relatively low population frequency (n = 4 in this cohort) of met homozygotes (Hariri et al. 2003). Genotypes were in Hardy-Weinberg Equilibrium ($Chi^2 = 3.21$, n.s). All participants gave written informed consent to take part in the study, and appropriate ethics clearance was obtained. Detailed demographics are in Table 6.2.1 below.

| Group | Number | Age (SD) | NART (SD) | Males (Females) | Right Handed (Left Handed) |
|---|---|---|---|---|---|
| Val Homozygotes | 28 | 31.9 (7.9) | 116.4 (6.8) | 15 (13) | 27 (1) |
| Met Carriers | 14 | 28.6 (5.1) | 116.5 (6.7) | 7 (7) | 14 (0) |

**Table 6.2.1 Demographic Details for Participants**

### 6.2.2 Genotype Analysis

Genotype at SNP rs6265 was determined for each included participant, using genomic DNA isolated from a venous blood sample. The genotyping used standard TaqMan assays, by the TaqMan polymerase chain reaction (PCR) based method (TaqMan, AssayByDesign, Applied Biosystems, Foster City, California). The Assay ID for the genotyping was C__11592758_10 and the context sequence is TCCTCATCCAACAGCTCTTCTATCA[C/T]GTGTTCGAAAGTGTCAGCCAAT GAT. This testing was conducted at the Wellcome Trust Clinical Research Facility, Edinburgh, United Kingdom (www.wtcrf.ed.ac.uk).

### 6.2.3 Experimental Design

Neural processing for social cognition during a task which targeted approachability judgment from faces was compared between both groups. The task consisted of three conditions: approachability, gender and baseline. In the approachability condition, participants were presented with facial images and asked to rate the faces as 'very approachable' or 'not approachable'. The facial images were of non-famous adults previously rated for approachability by separate healthy volunteers (for further details, see chapter 2). In the gender condition, participants were asked to indicate

the gender from the same facial images as used in the approachability condition. During baseline blocks participants were instructed to look at a fixation cross for 12.5 seconds. The task had a consisted of a two runs of six blocks each, alternating blocks between approachability judgment and gender judgment, with the order of the blocks being counterbalanced across participants. Each block was 25 seconds in duration, with each face being presented for 3.5 seconds separated by a 0.5 seconds inter-stimulus interval (ISI). There were 12.5 seconds long baseline periods between blocks during which participants were instructed to fixate on a cross in the centre of the screen. The dichotomized choices 'not approachable' and 'very approachable' were shown on the screen. Participants had to press one of two buttons to indicate their response.

### 6.2.3 Behaviour Evaluation within Scanner

Responses were scored against the rating for the picture which had been previously assigned as described above, with a maximum score of 36 in each category. Response times were recorded for all judgments made in the scanner. Task performance was controlled for using these measures.

### 6.2.4 Imaging

The fMRI image acquisition was performed as described in Chapter two.

### 6.2.4 Image Analysis

The acquired images were analysed The fMRI image acquisition was performed as described in Chapter two.

### 6.2.6 Connectivity Analysis

Connectivity analysis was performed using psycho-physiological interaction (PPI), as described in Chapter two.

## 6.3. Results

### 6.3.1 Demographics

Met carriers did not differ from the val homozygotes for any of the demographic measures, as summarized in Table 6.2.1 (Age: F1,40 = 0.577, P = 0.217, IQ as measured by the National Adult Reading Test (NART IQ) (Nelson and Willison 1991): F1,40 = 0.125, p = 0.725, Gender: F1,40 = 0.046, p = 0.832).

### 6.3.2 Difference in Emotional Behaviour between Groups

Within scanner behaviour measures of approachability and gender discrimination showed no significant difference in making gender or approachability judgements between the groups.

### 6.3.3 Effect of Genotype on Neural Response

All subjects were found to have performed the task in the scanner. Comparing brain activation between val homozygotes and met allele carriers for the approachability versus gender contrast (thresholded at $p < 0.005$, uncorrected), some bilateral amygdala over-activation in the met allele carriers was found using a bilateral amygdala SVC, but this difference was not statistically significant. Met allele carriers were found, however, to significantly over-activate a cluster with peak activation in the middle occipital gyrus ($P_{corr} = 0.002$, $K_E = 1205$, Peak T = 5.03, coordinates = -

50, -82, -12), also extending over parts of the inferior occipital gyrus, middle and inferior temporal gyrus. See Figure 6.3.1, Table 6.3.1 below.

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| 0.002 | 1205 | 5.03 | -50, -82, -12 | Left Occipital Gyrus |

**Table 6.3.1 Regions Showing Increased Activation in Met Carriers**

This table shows the regions with significantly increased activation in met carriers, compared to val overactivated by the met allele carriers, compared to the val homozygotes (val-val < val-met + met-met), for the approachability versus gender contrast, thresholded at $p < 0.005$, uncorrected.

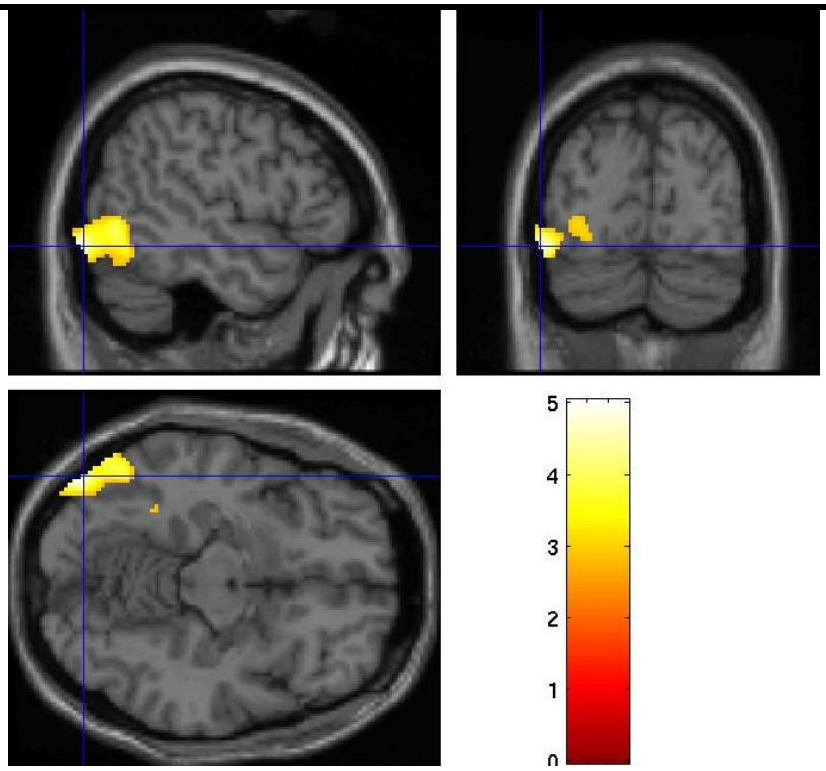



**Figure 6.3.1 Regions Showing Increased Activation in Met Carriers**

This figure is a SPM illustrating the regions with increased neural activation in met allele carriers as compared to the val homozygotes (val-val < val-met + met-met), for the approachability versus gender contrast, The figure is a SPM with regions with significantly decreased activation shown in yellow, thresholded at $p < 0.005$, uncorrected. Extent threshold 500 voxels. The cross hairs are at MNI coordinates -50, -82, -12.

### 6.3.4 Effect of Genotype on Connectivity

We examined the effective connectivity from the left and right amygdala (to the whole brain) corresponding to the approachability versus gender contrast. Examining the difference in connectivity between the groups, the met allele carriers showed significantly reduced effective connectivity from the left amygdala to a large cluster with peak in the right parahippocampal gyrus and also extending over parts of the hippocampus, thalamus and insula (Pcorr < 0.001 , KE = 1162, Peak T = 4.82, coordinates = 18 -26 -4), and another large cluster with peak in the medial frontal gyrus, also extending over parts of the middle and superior frontal gyrus (Pcorr = 0.001, KE = 959, Peak T = 4.14, coordinates = 14 2 68), a cluster extending over the left pre and post central gyrus ($P_{corr}$ = 0.005, $K_E$ = 752, Peak T = 4.55, coordinates = -50 -12 52), a cluster extending over parts of the left cerebellum, posterior cingulate and dentate gyrus ($P_{corr}$ = 0.010, $K_E$ = 670, Peak T = 4.49, coordinates = -14 -60 -30), a cluster with peak in the posterior cingulate also extending over parts of the lingual, para-hippocampal and occipital gyrus ($P_{corr}$ = 0.035, $K_E$ = 521, Peak T = 4.37, coordinates = -18 -52 -2) and a large cluster extending over parts of the superior and middle temporal gyrus and insula ($p_{corr}$ = 0.002, $K_E$ = 858, Peak T = 4.81, coordinates = -60 -14 0) (See Table 6.3.2, and the brain regions are shown in Figure 6.3.2).

No significant differences in connectivity were found from the right amygdala coordinate between the val homozygotes and the met allele carriers. Also, no brain regions were found to have significantly higher connectivity to the left amygdala for the met allele carriers, compared to val homozygotes.

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| P < 0.001 | 1162 | 4.82 | 18 -26 -4 | Parahippocampal Gyrus |
| 0.002 | 858 | 4.81 | -60 -14 0 | Superior and Middle Temporal Gyrus |
| 0.005 | 752 | 4.55 | -50 -12 52 | Pre and post central gyrus |
| 0.010 | 670 | 4.49 | -14 -60 -30 | Cerebellum and Posterior Cingulate |
| 0.035 | 521 | 4.37 | -18 -52 -2 | Posterior Cingulate |
| 0.001 | 959 | 4.14 | 14 2 68 | Medial Frontal Gyrus |

**Table 6.3.2 Reduced Connectivity in Met Carriers from Left Amygdala**

This table shows the regions with significantly lower effective connectivity from the left amygdala, corresponding to the approachability versus gender contrast, at threshold 0.005, uncorrected, in met allele carriers as compared to the val homozygotes (val-val > val-met + met-met).

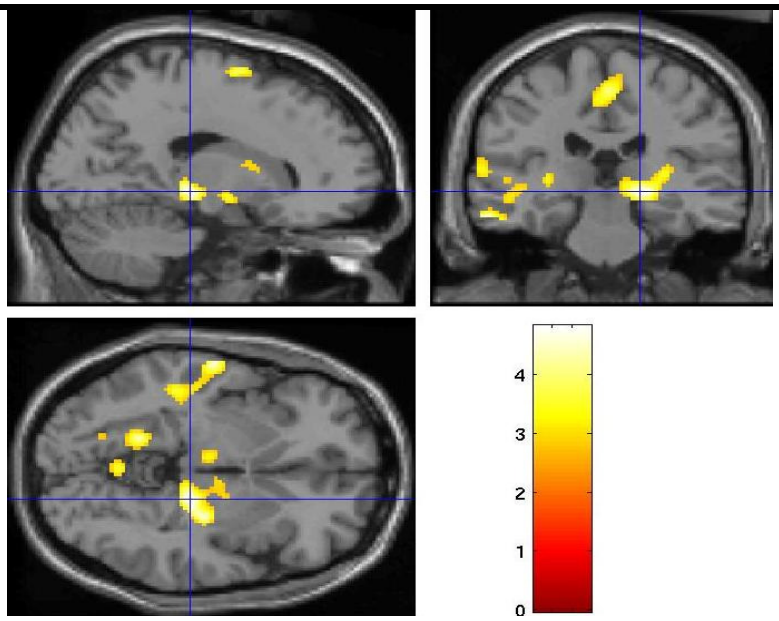



**Figure 6.3.2 Reduced Connectivity in Met Carriers from Left Amygdala**

This figure is a SPM illustrating regions with significantly lower effective connectivity, from the left amygdala, corresponding to the approachability versus gender contrast, at threshold 0.005, uncorrected, in met allele carriers as compared to the val homozygotes (val-val > val-met + met-met). Regions with significantly decreased connectivity are in yellow. Extent threshold 500 voxels. Cross hairs at 18 -26 -4. Figures 5 and 6 in the appendix show the additional clusters in Table 6.3.2

### 6.3.5 Correlation of Connectivity with Behaviour and Traits

Correlation analysis was performed to assess whether connectivity calculated above was related to trait measures SQ and EQ. Further, correlation analysis was also performed to assess whether connectivity was related to measures of within scanner approachability and gender judgment performance or response times for all participants. None of these correlations were significant, and neither were there any significant differences in these measures between groups.

## 6.4. Discussion

When making approachability evaluations, compared to gender evaluations, individuals carrying a met allele in the BDNF val66met SNP demonstrated increased activations in the occipital gyrus, as well as the middle and inferior temporal gyrus, brain regions not specifically associated with social cognition and face processing.

For the approachability versus gender contrast, individuals with a met allele demonstrate reduced effective connectivity from the left amygdala to a large cluster with peak in the right parahippocampal gyrus and also extending over parts of the hippocampus, thalamus and insula as well as another large cluster with peak in the medial frontal gyrus, also extending over parts of the middle and superior frontal gyrus. Further, met allele demonstrate reduced effective connectivity from the left amygdala to a cluster with peak in the posterior cingulate also extending over parts of the lingual, para-hippocampal and occipital gyrus, as well as clusters extending over the left pre and post central gyrus, left cerebellum, posterior cingulate, dentate gyrus, and the superior and middle temporal gyrus and insula.

As described earlier, the amygdala is believed to play a key role in evaluating the emotional salience of social stimuli (Bickart et al., 2010, Vuilleumier & Pourtois, 2007, Adolphs, 2003, Baron-Cohen, 2003, Brothers, 1990), and be a major hub in the networks for social and emotional processing (Benes 2010). Here the met allele carriers were found to show reduced connectivity from the amygdala to several brain regions linked to social cognition and facial affect processing (Haxby et al., 2002, Phillips et al., 2003a,b, Adolphs 2002). In particular, the medial prefrontal cortex (MPFC) (Sprengelmeyer et al., 1998, Damasio et al., 1990, Sotres-Bayon and Quirk,

2010) is suggested to regulate the expression and extinction of emotion, and has been associated with theory of mind as well as self-control and other executive functions (Fletcher at al, 1995a, Happe et al., 1996, Gallagher et al., 2000, Adolphs, 2001) and social judgement (Amadio and Frith, 2006). Further, both the MPFC and the posterior cingulate cortex have been associated with social cognition (Brothers, 1990, Adolphs, 2001, Adolphs, 2003, Amadio and Frith, 2006). The superior temporal and lingual gyrus have been demonstrated to be involved in processing facial expression and direction of gaze (Brothers, 1990, Adolphs, 2001, Haxby et al., 2000, Kemotsu, et al., 2005, Allison et al., 2000). The insula has been shown to be involved in processing empathy (Singer et al., 2004a), and evaluating the emotional state of another individual from their facial expression (Adolphs, 2001). Additionally, the cerebellum has also been associated with in social function (Schmahmann and Sherman 1998, Schmahmann 2004). Therefore the met allele carriers show disconnectivity between the amygdala and several parts of the social brain, or the brain network associated with processing socio-affective stimuli (Haxby et al., 2002, Adolphs 2001).

Many of these regions are known to be inter-connected, and the posterior cingulate cortex and precuneus, are believed to be major functional hubs in the brain (Tomasi and Volkow, 2010a,b). The STG also connects to the thalamus, hippocampus and amygdala, as well as neocortical association areas in the prefrontal cortex (Matsumoto et al., 2004).

Additionally, BDNF has previously been shown to impact upon structural and functional abnormalities in the insula (Escobar, 2003), as well as with the amygdala and hippocampus, discussed in detail below.

In general, the BDNF protein plays a key role in synaptic plasticity (Poo 2001, Lu 2003). The substitution of a met allele in the val66met SNP of the human BDNF gene diminishes activity dependent secretion of BDNF (Egan et al. 2003, Chen et al. 2006). Therefore carrying a met allele in the SNP would be expected to have impact upon synaptic plasticity. Synaptic plasticity underlies connectivity, which is suggested to be a core aspect of the pathology of schizophrenia (Friston, 1998). Therefore this variant might be associated with decreased connectivity. Therefore the reduced connectivity in met allele carriers is in keeping the disconnection hypothesis of schizophrenia.

Arguably the most interesting result of this study might be the disconnectivity between the amygdala and the hippocampus. It has been suggested that the amygdala might be responsible for associating affective significance to perceptual input, and therefore with encoding, storage and retrieval of these in memory (Anticevic et al., 2011, Markowitsch and Staniloiu, 2011). BDNF affects emotional learning in the amygdala (Hall et al., 2000, Rattiner et al., 2005, Rattiner et al., 2004, Rattiner et al., 2005, Chhatwal et al., 2006, Jones et al., 2007, Monfils et al., 2007, Ou and Gean 2007, Yee et al., 2007). BDNF val66met SNP met allele carriers show functional and structural amygdala abnormalities (Montag et al., 2008, Montag et al., 2009, Lau et al., 2010).

The hippocampus is crucial for learning and memory (Green, 1964, Belyĭ, 1966). Genetic variation in BDNF has been extensively linked to structural and functional abnormalities in the hippocampus (Patterson 1992), particularly with respect to emotional and contextual memory (Korte et al., 1998, Hall et al., 2000, Lau et al., 2010). Carriers of the met allele of the val66met SNP showed structural abnormalities in the hippocampus (Bueller et al., 2006, Frodl et al., 2007, Montag et al., 2009). Functional imaging studies showed that met allele carriers overactivated the hippocampus in various episodic memory tasks (Egan et al., 2003, Hariri et al., 2003, Chen et al., 2006) and behavioral studies have shown met allele carriers to have impaired associative learning of aversive cues (Hajcak et al., 2009). BDNF is known to impact plasticity and learning in the hippocampus (Lu and Gottschalk, 2000) and BDNF deletion in the hippocampus effects aversive memory (Heldt et al., 2007).

Therefore, the disconnection shown here between the amygdala and hippocampus might impede emotional learning, as well as retrieval of socio-affective information, in this study related to approaching other individuals.

Rodents show an impact of peer interaction on levels of neural plasticity markers such as BDNF, as well as adult social competencies (Branchi et al., 2009). Mouse models have shown that BDNF plays a role in learning from social defeat, and appropriate wariness of strangers after aversive encounters (Berton and Nestler, 2005). Early experiences such as maternal deprivation affect BDNF levels, and psycho-social stress, such as aggressive interactions, in adults alters BDNF levels

both in plasma and in the hippocampus in mice, as well as humans (Branchi et al., 2004, Castren et al., 2007).

Social experience is a major epigenetic factor and this impact of early life psycho-social stress on BDNF levels, as well as activity dependant BDNF secretion, might have long term effects on synaptic plasticity. This could impairing the ability to cope with novel and stressful situations, thereby increasing vulnerability to psychopathology, depending on other genetic and environmental factors (Zubin and Spring, 1977, Cirulli et al., 2010, Alleva and Francia, 2009).

BDNF is associated with vulnerability to a wide range of psychiatric disorders, with a common component of mood regulation and socio-affective behaviour abnormalities (Hashimoto et al., 2004, Hashimoto 2007, Gatt et al., 2009, Jindal et al., 2010, Egan and Weinberger 1997, Hall et al., 2007, Lu and Martinowich, 2008, Neves-Pereira et al., 2005, Muglia et al., 2002, Le Strat et al., 2009, Rybakowski 2008, Angelucci et al., 2005, Shoval and Weizman, 2005). However, it is not clear how this association is mediated (Groves et al., 2007 and Martinowich, Manji and Lu 2007). The disconnection corresponding to social judgement shown in the present study might be relevant to the processes underlying aberrant social behaviour in schizophrenia, and reflect the impact of BDNF on learning from previous social experience which might in turn modulate future social behaviour.

To summarize, the present study demonstrated functional disconnection in met allele carriers of the BDNF val66met polymorphism, in keeping with the reduced activity dependant secretion of BDNF in these populations, which would

impact synaptic plasticity, and hence connectivity. Moreover, this disconnection involves key regions for affective function and memory. Given the role of BDNF in assimilation and retrieval of information from aversive social experience, this might illustrate an important way in which this BDNF induced disconnection manifests in the relevant functional network to impact behaviour. This might therefore mediate the impact of the BDNF val66met SNP on vulnerability to affective psychopathology, including schizophrenia, where gross behavioral abnormalities are found in related aspects of social cognition and emotional function. We do not have enough power, however, to examine gene by group contrasts in the current dataset, therefore in this study the variation of effective connectivity with the BDNF gene in patients could not be investigated. This important topic might be of interest for future studies. Further, in this study we did not find any correlations between effective connectivity and behavioral measures. However, future studies might examine such a correlation using more relevant measures, such as trait anxiety.

# CHAPTER SEVEN:

# Discussion

## 7.1 Introduction

In Chapter one I discussed the persisting challenges in charactering the physical basis for schizophrenia, and the lack of a unified theory comprehensively defining the underlying pathology. Therefore all findings regarding the physiological differences in schizophrenia are extremely valuable.

The disconnection hypothesis posits that disconnection, or abnormal interaction between different neural systems, is a core feature of the pathology of schizophrenia. Individuals with schizophrenia commonly demonstrate abnormal socio-emotional behaviour, and further these brain functions are believed to be sub-served by distributed brain networks. Therefore, as discussed in section 1.8, I hypothesised that the brain networks underlying social and emotional behaviour might show disconnection in individuals with schizophrenia, which in turn might mediate the socio-emotional behavioural abnormalities associated with the disorder.

Further, schizophrenia is highly heritable, with a polygenic aetiology, and complex interactions between several genes and environmental factors are believed to determine disease manifestation. One of the many genetic factors associated with schizophrenia, BDNF is also strongly associated with plasticity, and thereby likely to impact neural connection. It has been linked to both social and emotional learning, as described in Chapters five and six respectively, as well as with stress, one of the key environmental factors referred to in gene by environment, or 'two-hit' models of schizophrenia. Met allele carriers of the BDNF val66met SNP have been shown to have lower BDNF levels. Therefore I additionally hypothesised that the BDNF

val66met SNP met allele carriers would also show similar patterns of disconnectivity as individuals with schizophrenia, as described in section 1.8.

In Chapters three to six I demonstrated disconnectivity in schizophrenia for the first time in a social judgement task, as well as on an emotional processing task, using a standard methodology and seed region, as well as similar populations (for details, see Chapter two). Further, I show similar pattern of disconnection in individuals carrying the met allele of the BDNF val66met SNP. Thus I support the hypotheses of the present study, of reduced connectivity in patients, as well as in carriers of the met allele of BDNF for a set of socio-emotional tasks (for details Section 1.8), and present a specific manifestation of disconnection, which is proposed to be a core physiological feature of schizophrenia.

In this Chapter I first highlight the key results from Chapter three to Chapter six, and then I discuss the significance and implications of these findings. As each of the individual experimental chapters ends with a detailed discussion of the findings therein, this general discussion chapter does not elaborate on these, only repeating the key points relevant for understanding. Finally I shall discuss limitations of the present work, as well as possible future directions.

## 7.2. Summary of Findings

The key findings of the study have been illustrated in table 7.2.1, 7.2.2 and 7.2.3 below, showing the differences in activation patterns, connectivity and behaviours found in the present study.

The over-arching finding is reduced connectivity in individuals with schizophrenia, from the bilateral amygdala to key nodes in socio-emotional information processing networks. Further, individuals with schizophrenia demonstrated increased activation in several brain regions which are not usually associated with the task, and which were not recruited by healthy controls in the present study. This over-activation of task unrelated brain regions maybe be a compensatory mechanism for disconnection within task related networks, as also found in studies of other brain functions in schizophrenia (Tan et al., 2006).

### 7.2.1 Findings for Fear Processing in Schizophrenia

In the fear processing experiment, that is while making gender judgements from fearful, as compared to neutral faces, individuals with schizophrenia demonstrated reduced effective connectivity between the left amygdala and regions including the right precuneus and tempero-parietal junction (TPJ). Further, individuals with schizophrenia demonstrated reduced brain activation in the left amygdala, right lingual gyrus and right superior temporal gyrus.

### 7.2.2 Findings for Approachability Judgement in Schizophrenia

In the social judgement task, that is while making approachability as compared to gender judgements, individuals with schizophrenia demonstrated reduced effective connectivity between the right amygdala and the right inferior frontal gyrus, right insula, right superior temporal gyrus, as well as between the left amygdala to parts of the right thalamus, right insula, right para-hippocampal gyrus and right inferior frontal gyrus. Further, individuals with schizophrenia showed increased brain activation in the right precuneus, right inferior and superior parietal gyrus, right supra marginal, right superior temporal gyrus, the right inferior, middle and superior frontal gyrus.

### 7.2.3 Effect of Variation in BDNF on Fear Processing

A similar pattern of reduced connectivity was found in met allele carriers of the BDNF val66met SNP. In the fear processing experiment, that is while making gender judgements from fearful, as compared to from neutral faces, met carriers demonstrated reduced effective connectivity between the anterior cingulate cortex (ACC) to para-hippocampal gyrus (PHG) compared to val homozygotes. Further, they demonstrated increased activation in the medial ACC as well as the bilateral insula. No significant connectivity differences were found from bilateral amygdala.

### 7.2.4 Effect of Variation in BDNF on Approachability Judgement

In the social judgement task, that is while making approachability judgements, as compared to gender judgements, met allele carriers demonstrated reduced connectivity from the left amygdala to clusters extending over the right hippocampus

and parahippocampal gyrus, thalamus, insula, medial, middle and superior frontal gyrus, as well as the left pre and post central gyrus, cerebellum, posterior cingulate, dentate gyrus, lingual, para-hippocampal, occipital gyrus, superior and middle temporal gyrus and insula, compared to val homozygotes. Further, the met allele carriers showed increased activation in a cluster extending over parts of the left middle and inferior occipital gyrus as well as the middle and inferior temporal gyrus.

| | **Fear** versus **Neutral** | **Approachability** versus **Gender** |
|---|---|---|
| **Patients** versus **Controls** | • Reduced Activation in the Right lingual gyrus<br>• Reduced Activation in the Right superior temporal gyrus<br>• Reduced Activation in the Left amygdala (with SVC)<br>• **Chapter 3** | • Increased activation in right precuneus, extending over inferior and superior parietal gyrus, supra marginal and superior temporal gyrus.<br>• Increased activation in right inferior frontal gyrus, extending over the middle and superior frontal gyrus<br>• **Chapter 4** |
| **Met** Carriers versus **Val homozygotes** | • Increased activation in ACC and PFC<br>• Increased activation in brain stem and cerebellum<br>• Increased activation in left insula<br>• Increased activation in right insula<br>• **Chapter 5** | • Increased activation in middle occipital gyrus, also extending over parts of the inferior occipital gyrus, middle and inferior temporal gyrus<br>• **Chapter 6** |

**Table 7.2.1 Activation Differences between Groups**

| | Fear versus Neutral | Approachability versus Gender |
|---|---|---|
| **Patients** versus **Controls** | • Decreased connectivity from left amygdala to right TPJ, extending over the inferior parietal lobe, superior and middle temporal gyrus and superior parietal gyrus<br>• **Chapter 3** | • Decreased connectivity from right amygdala to right inferior frontal gyrus, extending over insula and superior temporal gyrus<br>• Decreased connectivity from left amygdala to right PHG<br>• Decreased connectivity from left amygdala to right inferior frontal gyrus, extending over insula and thalamus<br>• **Chapter 4** |
| **Met** Carriers versus **Val homozygotes** | • No significant differences from amygdala<br>• Decreased connectivity from ACC to hippocampus and PHG<br>• From the left and right insula to regions in the cerebellum<br>• No significant differences from brainstem<br>• **Chapter 5** | • From the left amygdala to right brainstem and PHG, right SMA and MFG, left MTG and STG, left pre and post central gyrus, left cerebellum, posterior cingulate, left lingual gyrus<br>• **Chapter 6** |

**Table 7.2.2 Connectivity Differences between Groups**

| | For Fear Processing Task | For Approachability Judgement Task |
|---|---|---|
| **Patients** versus **Controls** | • For all participants, no performance difference in scanner, behaviour testing, or significant correlation between connectivity and these performance parameters<br>• For patients significant correlations of connectivity with PANSS Abstract Thinking. No significant correlation with medication<br>• **Chapter 3:** | • For all participants, no performance difference in scanner, or correlation between connectivity and these performance parameters<br>• For patients trend to significant correlations of connectivity with PANSS Abstract Thinking. No significant correlation with medication<br>• **Chapter 4:** |
| **Met** Carriers versus **Val homozygotes** | • No performance difference in scanner, or correlation with connectivity<br>• Behaviour testing out of scanner showed reduced ability to identify emotion of fear in met allele carriers.(co-varying for age and NART IQ - both of which were found to independently influence fear recognition)<br>• **Chapter 5** | • No performance difference in scanner, or correlation with connectivity<br>• **Chapter 6:** |

**Table 7.2.3 Behaviour, Correlations with Symptoms & Medication**

## 7.3 Discussion of the Key Results

### 7.3.1 Fear processing in Individuals with Schizophrenia

In this section I briefly discuss the most important differences in brain activation, and amygdala connectivity found in individuals with schizophrenia for the fear task. Patients were found to underactivate the right superior temporal gyrus, right lingual gyrus and left amygdala compared to controls. These regions have been associated with emotional processing, particularly from faces (Haxby et al., 2002, Phillips et al., 2003). Most importantly, the amygdala plays a central role in social cognition (as reviewed in Adolphs, 2010), and recognizing emotion from faces (Adolphs, 2002). It is particularly relevant for fear processing (LeDoux 2003). The amygdala has connections to multiple perceptual and cognitive regions (Phelps and LeDoux, 2005). Further, the amygdala has been repeatedly implicated in schizophrenia, as being abnormal in structure, function and connectivity, as reviewed in Aleman and Kahn, 2005, Kucharska-Pietura et al., 2003, Shayegan and Stahl, 2005 as well as Marwick and Hall, 2008. Specifically, patients with left amygdala damage show social function deficits (Fine et al., 2001).

For fear processing, compared to controls, patients show reduced connectivity between the amygdala and the TPJ, as well as the precuneus, both brain regions associated with Theory of Mind (TOM) and mentalizing (Saxe and Powell, 2006, Brass et al., 2005, Perner et al., 2006, Saxe, 2006, Saxe and Kanwisher, 2003, Young and Saxe, 2008, 2009, Aichhorn et al., 2006, Mar, 2011, Fletcher at al., 1995b). Functional abnormalities in the TPJ for theory of mind have also been reported in schizophrenia (Benedetti et al., 2009, Vistoli et al., 2011). Additionally, network

simulation studies have found that lesions in the TPJ are more disruptive to overall connectivity in models, compared to other regions (Alstott et al., 2009), which implies this is an important connectivity hub in the brain. Further, the precuneus is also believed to be a major connectivity hub in the brain (Tomasi et al., 2010, Tomasi et al., 2011). Therefore, this disconnection might impact a patient's ability to think about others, with respect to fear and therefore mediate behaviours such as paranoia and persecutory delusions.

### 7.3.2 Approachability Judgement in Individuals with Schizophrenia

While making approachability judgements, as compared to gender judgements, key regions for social function and facial affect processing were found to be overactivated by the individuals with schizophrenia (Adolphs, 2001, Haxby et al., 2002). Most importantly individuals with schizophrenia showed increased activation in the inferior frontal gyrus (IFG) and reduced connectivity from the amygdala to the precuneus and IFG.

The precuneus is associated with self related processing, or taking a first person perspective and mentalizing (Cavanna and Trimble, 2006, Mar, 2011, Fletcher at al., 1995b). The IFG plays an inhibitory role in making decisions related to risk (Knoch et al., 2006), and activity in IFG correlates with personality differences in risk aversion (Christopoulos, et al., 2010). Therefore the IFG overactivation, as well as reduced connectivity between the IFG and amygdala in individuals with schizophrenia could reflect an increased sense of threat to themselves while assessing approachability in faces of others.

This disconnection might therefore impact upon the assessment of self related social risk. Functional abnormalities have been reported in these brain regions during

social cognition in schizophrenia (Li et al., 2010, Habel et al., 2010, Hall et al., 2004, Lepage et al., 2011, Kumari et al., 2010, Rylands et al., 2011). Fronto-temporal connectivity for social cognition between regions including the ones indicated in the present study has been shown (White et al., 2010, Lee et al., 2004).

Interestingly, both the amygdala and the precuneus are known to be major connectivity hubs in the brain (Tomasi et al., 2010, Tomasi et al., 2011, Phelps and LeDoux, 2005), and white matter abnormalities have also been reported for these regions in schizophrenia (Antonius et al., 2011).

### 7.3.4 Effect of Variation in BDNF on Fear Processing

In response to fearful faces, met allele carriers of the BDNF val66met SNP, compared to val homozygotes, demonstrated increased activation in brain regions involved in regulation of the autonomic nervous system (Critchley 2009). Previous studies have also shown that BDNF val66met SNP can influence autonomic responses including responses to emotional stimuli (Gatt et al., 2009).

Genetic variation in BDNF has been associated with structural and functional abnormalities in the hippocampus (Patterson 1992, Egan et al., 2003, Bueller et al., 2006, Montag et al., 2009). Functional abnormalities have been shown in the hippocampus for contextual memory (Korte et al., 1998, Hall et al., 2000, Heldt et al., 2007, Lau et al., 2010), as well as episodic memory tasks (Egan et al., 2003, Hariri et al., 2003, Chen et al., 2006). Further, structural abnormalities have also been shown in the hippocampus (Bueller et al., 2006, Frodl et al., 2007, Montag et al., 2009). Additionally, the ACC is associated with cognitive control of emotions (Allman et al., 2001). Structural and functional abnormalities have also been reported in the insula (Escobar, 2003) and anterior cingulate cortex (ACC) in relation to BDNF (Lang et al.,

2007, Takahashi, 2000, Gallinat et al., 2010). This overactivation might therefore show heightened autonomic response to fear in met allele carriers, whereas the disconnection between ACC and hippocampus might affect cognitive regulation of fear related learning and memory (Hartley and Phelps, 2010). This important connection might be necessary to recall familiar social stimuli, and thus mediate the effect of BDNF on anxiety and fear related behaviour (Montag et al., 2008, Chen et al., 2006.

### 7.3.5 Effect of Variation in BDNF on Approachability Judgement

During the approachability task the most striking result in individuals with a met allele in the BDNF val66met SNP was a reduced effective connectivity from the amygdala to the hippocampus as well as to the precuneus.

The effects of BDNF are particularly pronounced in the hippocampus, a region crucial for learning and memory (Green, 1964, Belyĭ, 1966). Further, it has been suggested that the amygdala might be responsible for associating affective significance to perceptual input, and therefore interact with encoding, storage and retrieval of these in memory (Anticevic et al., 2011, Markowitsch and Staniloiu, 2011). Additionally, met carriers show reduced connectivity to the precuneus, which as well as being a major connectivity hub in the brain, affects first person perspective taking, as described in the previous section.

As discussed in Chapter six, studies of BDNF mouse models with BDNF deletion showed that this protein is necessary for learning appropriate wariness of strangers after experiencing social defeat (Berton and Nestler, 2005). Such social learning from past experiences would be likely to critically impact future social behaviour, such as approachability judgement. Therefore the disconnection between

the amygdala and hippocampus shown in Chapter six might reflect this effect of BDNF on social learning.

## 7.4 Implications of the Results for Connectivity in Schizophrenia

As described in Chapter one, the disconnection hypothesis suggests disconnectivity to be a core pathophysiological feature of schizophrenia (Friston, 1998, Stephan et al., 2009). Abnormal connectivity has been demonstrated in schizophrenia for varied functions including working memory, verbal tasks, saccadic variance, default mode network activity, emotion processing, and affect recognition. Some of these are reviewed in Whalley et al., 2009. Connectivity for social judgement in schizophrenia, however, has not been investigated previously, as mentioned in Chapter four. Despite extensive investigation of connectivity in schizophrenia, comparing the findings from different studies is complicated by methodological differences between individual investigations, as discussed in detail in Chapter one. Nevertheless, a strong trend of reduced connectivity in schizophrenia emerges from most of these studies (Pettersson-Yeo et al., 2011, Lynall et al., 2010).

The concepts behind connectivity originated with the analysis of separable spike trains from multi-unit recordings (Aerston and Preissl, 1991, Gerstein and Perkel, 1969). More recently this has been generalised to relationships between neurons, or neuronal systems, as the method of examination evolved from single cell and dissection, to multi-unit recording, to EEG, PET and fMRI (Volkow et al., 1988, Weinberger et al., 1992, Friston and Frith, 1995, Friston, 1996, Bullmore et al., 1997, Lynall et al., 2010, McIntosh and Gonzalez-Lima, 1994, Horwitz et al., 1998). Despite several ways of defining functional or effective connectivity conceptually, as well as several methods of estimating them, the exact neurobiological basis of such connectivity remains unclear (Horwitz, 2003, Horwitz et al., 2005). It does not require

direct anatomical connectivity, and indeed relevance of structural versus functional investigation for understanding of brain function has been questioned (Lee et al., 2003).

Further, it is not clear how these definitions of connectivity translate across modalities, but within fMRI these terms focus on "description of patterns of neural activity", rather than "explanations of their origins" (Lee et al., 2003). Therefore functional or effective connectivity refers to behavior between two collections of neurons, or neuron-like circuits, and therefore does not presume anatomic connections, because the same behaviour could be produced by neurons connecting in different ways (Horwitz, 2003). Additionally, in fMRI, how the observed BOLD signal relates to the underlying neural activity, and how biological factors such as CSF and heart-rate interact with these measurements, and connectivity, is also unclear (Heeger and Ress, 2002, Logothetis, 2008, Maldijan, 2001, Rogers et al., 2007).

It is generally agreed however, that functional connectivity is defined as the "temporal correlations between spatially remote neurophysiological events" (Friston et al., 1993) and effective connectivity, sometimes referred to as a specialisation of functional connectivity, indicates the change in influence of a neuronal system over another but does not necessarily indicate causality (Friston, 1994). Such connectivity depends on factors such as synaptic plasticity and neurotransmission (Friston, 1998, Stephan et al., 2009). Electrical activity related to neurotransmitters affects synaptic transmission, and thereby modulates neural circuits in the brain in a dynamic fashion, enabling learning and adaptation (Zhang and Poo, 2001). Such connectivity has been shown to vary with task load (Rowe et al., 2002) as well as with physiological factors such as cardiac and respiratory factors (Birn et al., 2006, Bhattacharyya et al., 2004).

A study examining correlations in low frequency fluctuations in the inter-hemispheric auditory cortex compared between a subject with callosal agenesis and a healthy subject demonstrated reduced functional connectivity, therefore validating the concept of functional connectivity (Lowe et al., 1997). Connectivity has been shown to be impacted by drugs (Li et al., 2000) and antipsychotic medication via synaptic plasticity (Stephan et al., 2001).

## 7.5 Implications of the Results for Associations between Schizophrenia and BDNF

Schizophrenia is believed to have a polygenic aetiology (Lang et al., 2005, Keshavan et al., 2008, Sun et al., 2008), with epigenetic and environmental factors interacting in complex ways to influence disease manifestation (Lawrie et al., 2008, Tsuang et al., 2000, Benes et al., 1997, Palomo et al., 2004).

Although BDNF is not the strongest candidate amongst risk genes for schizophrenia, it impacts upon synaptic plasticity, and thereby is likely to affect connectivity, a core aspect of the pathology of schizophrenia (Friston, 1998, Stephan et al., 2009). Several studies have investigated the association between BDNF and schizophrenia (Jindal et al., 2010, Egan and Weinberger 1997, Hall et al., 2007, Lu and Martinowich, 2008, Neves-Pereira et al., 2005, Muglia et al., 2002, Le Strat et al., 2009, Rybakowski 2008, Angelucci et al., 2005, Shoval and Weizman, 2005).

In support of this association, levels of the BDNF and its receptor TrkB have been shown to be reduced in several brain regions, particularly cortico-limbic, as well as in serum of individuals with schizophrenia (Toyooka et al., 2002, Buckley et al., 2007, Jindal et al., 2010, Thompson Ray et al., 2011, Weickert et al., 2003, Hashimoto et al., 2005, Takahashi et al., 2000). Further, animal models of schizophrenia show abnormal BDNF signalling (Angelucci et al., 2004), lesion models with BDNF reduced mRNA levels simulate schizophrenia-like phenotypes (Ashe et al., 2002, Lipska et al., 2001, Molteni et al., 2001), and post-mortem studies show decreased BDNF mRNA in individuals with schizophrenia (Durany et al., 2001, Weickert et al., 2003, Weickert et al., 2005, Hashimoto et al., 2005).

Additionally, BDNF impacts upon neurotransmitter systems such as dopamine, glutamate, serotonin and GABA (Shoval and Weizman 2005, Guillin et al., 2001, Carvalho et al., 2008, Mattson 2008), and regulate properties of NMDA channels (Levine et al., 1998), mechanisms which are believed to be affected in schizophrenia. Further, TrkB signalling is disrupted in individuals with schizophrenia, leading to decreased expression of GABA-related genes (Lewis et al., 2005). BDNF also has been shown to impact response to anti-psychotic drugs in schizophrenia (Lipska et al., 2001, Chlan-Fourney et al., 2002, Angelucci et al., 2005, Angelucci et al., 2000, Bai et al., 2003, Grillo et al., 2007, Xu et al., 2010, Chen and Huang, 2011).

Imaging studies of subjects at high risk for schizophrenia show increased neural activation, particularly in prefrontal and hippocampal regions (Whalley et al., 2010). As discussed in Chapter five, the met allele of the val66met, or rs6265, is a single nucleotide polymorphism (SNP) features diminished activity dependant secretion of BDNF. Therefore val66met SNP has been associated with schizophrenia (Craddock et al., 2006 and Gratacos et al., 2007, Numata et al., 2006, Chao et al., 2008). However, the reported associations of the BDNF val66met variant with schizophrenia have not been consistent (Kanazawa et al., 2007). Though all studies do not agree, many indicate the met allele for memory deficits in health, whereas the val allele is shown by many to be associated with risk for disorder (Martinowich, 2008). It has been suggested this might be due to complex interactions between multiple genes, and environmental factors (Pezawas et al., 2008).

As described in Chapter five, studying the effect of genes in patients is sometimes confounded by factors such as medication, disease duration and age of onset which have been shown to interact with BDNF (Chao et al., 2008, Angelucci et

al., 2005, Angelucci et al., 2000, Bai et al., 2003, Grillo et al., 2007, Xu et al., 2010, Chen and Huang, 2011). Complex interactions between several genes and environmental factors further complicate such investigation (Casey et al., 2010).

Stress, particularly social and emotional, is an important environmental factor indicated in gene-environment models (Lawrie et al., 2008, Palomo et al., 2004, Howes et al., 2004, Benes et al., 1997). Interestingly, BDNF has been related to the pathophysiology of stress (Colzato et al., 2011, Saruta et al., 2010), and BDNF levels have been shown to reduce under stress (Fuchikami et al., 2010).

In the present study I showed that within healthy individuals, carriers of the met allele of the BDNF val66met SNP to have similar physiological patterns as found in individuals with schizophrenia. This might reflect a predisposition to disease features, which in concert other genes, as well as environmental factors such as stress, determine disease manifestation.

## 7.6 Implications of the Results for the Association between Connectivity and BDNF

The BDNF protein plays a key role in synaptic plasticity (Poo 2001, Lu 2003), which in turn influences connectivity (Friston, 1994, Friston, 1998, Stephan et al., 2006, Stephan et al., 2009). The substitution of a met allele in the val66met SNP of the human BDNF gene diminishes activity dependent secretion of BDNF (Egan et al. 2003, Chen et al. 2006). Therefore, carriers of the met allele in the SNP would be expected to have impaired connectivity. This suggests that this variant might be associated with decreased connectivity, suggested to be a core aspect of the pathology of schizophrenia (Friston, 1998). Therefore the reduced connectivity in met allele carriers supports the disconnection hypothesis of schizophrenia.

As discussed in Chapter six, social stress is an important environmental factor in gene by environment models of disorder. Further, long term activity dependant secretion of BDNF, and therefore synaptic plasticity, has been shown to be impacted by social stress. Rodents show an impact of peer interaction on levels of neural plasticity markers such as BDNF, as well as adult social competencies (Branchi et al., 2009). Mouse models have shown that BDNF deletion induces deficits in learning appropriate wariness of strangers after aversive encounters and social defeat (Berton and Nestler, 2005). Early experiences such as maternal deprivation, and social stress in adulthood such as aggressive interactions, have been shown to alter BDNF levels both in plasma and in the hippocampus in mice (Branchi et al., 2004). In humans BDNF levels have been shown to be elevated in times of psycho-social stress (Castren et al., 2007). Reduced activity dependant BDNF secretion might have long term effects on synaptic plasticity, impairing the ability to cope with novel and stressful

situations, and thereby increasing vulnerability to psychopathology, together with other genetic and environmental factors (Zubin and Spring, 1977, Cirulli et al., 2010). This could mediate inter-individual differences in vulnerability to stress or psychiatric disorders (Alleva and Francia, 2009). This is illustrated in Figure 7.4.1 below.

BDNF is associated with vulnerability to a wide range of psychiatric disorders, many of which have a common component of mood regulation and socio-affective behaviour abnormalities (Hashimoto et al., 2004, Hashimoto 2007, Gatt et al., 2009) including schizophrenia (Jindal et al., 2010, Egan and Weinberger 1997, Hall et al., 2007, Lu and Martinowich, 2008, Neves-Pereira et al., 2005, Muglia et al., 2002, Le Strat et al., 2009, Rybakowski 2008, Angelucci et al., 2005, Shoval and Weizman, 2005). However, it is not clear how this association is mediated (Groves et al., 2007 and Martinowich, Manji and Lu 2007).

The disconnectivity for emotional and social functions shown in met allele carriers of the BDNF val66met SNP in the present study, which mimic the patterns of disconnectivity for similar functions shown in individuals with schizophrenia, might suggest that the interaction between this SNP and features of psychiatric disorder might be mediated by such disconnectivity.

Further, the associations between BDNF and disorder are believed to interact with other genetic, epigenetic and environmental factors to manifest illness. Due to the associations between BDNF and the physiological basis of reaction to stress, which might reflect individual differences in mechanisms for coping with stress, this might further contribute to the manifestation of disorders.

Further, the effect of variation in BDNF in response to fear processing, might mediate the effects of this SNP seen in affective psychiatric disorders, especially those

related to fear (Hashimoto et al., 2004, Martinowich et al., 2007). These effects on fear processing may provide a neural substrate for the effects of genetic variation in BDNF on susceptibility to higher trait anxiety or negative emotion in a general sense (Montag et al., 2008), and different psychiatric disorders, as discussed in Chapter five.

To summarize, the present study demonstrated functional disconnection in met allele carriers of the BDNF val66met polymorphism, in keeping with the reduced activity dependant secretion of BDNF in these populations, which would impact synaptic plasticity, and hence connectivity. Moreover, this disconnection involves key regions for affective function, memory, and autonomic response, which have are all brain functions which have been shown to be impacted with variation in BDNF.

Given the role of BDNF in assimilation and retrieval of information from aversive social experience, this might illustrate an important way in which this BDNF induced disconnection manifests in the relevant functional network to impact upon behaviour.

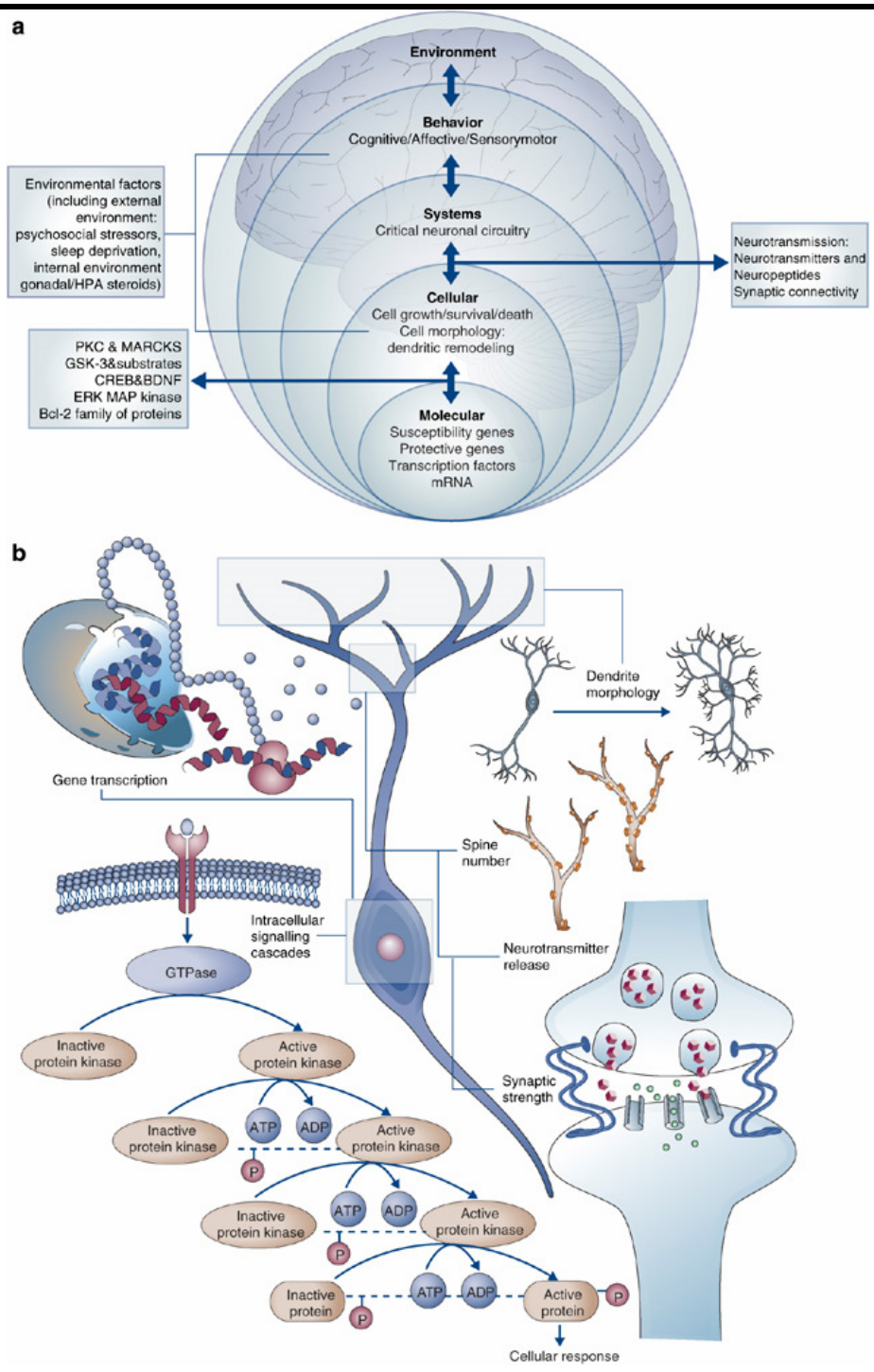



Figure 7.4.1 This diagram illustrates the effect of synaptic plasticity and how it cascades to behaviour (Figure from: Schloesser et al 2008). This shows Biological mechanisms underlying neuroplasticity. The remarkable plasticity of neuronal circuits is achieved through different biological means including alterations in gene transcription and intracellular signaling cascades. These changes modify diverse neuronal properties such as neurotransmitter release, synaptic function and even morphological characteristics of neurons.

## 7.7 Methodological Considerations of Estimating Connectivity by PPI

Several measures have been employed to estimate connectivity, as reviewed in Li et al., 2009, Rogers et al., 2007, (for details see Chapter one). Psycho-Physiological Interactions (PPI), which estimates change in effective connectivity corresponding to a change in psychological context, being therefore ideally suited for cognitive subtraction based fMRI paradigms, has relatively few implementations in schizophrenia (Boksman et al., 2005, Das et al., 2007, Fakra et al., 2008, Schlösser et al., 2009, Bakshi et al., 2011, Papagni et al., 2011, Harvey et al., 2011, Barbalat et al., 2011).

Kim and Horwitz (2008) investigated the neural basis of connectivity estimated with PPI, using a neural simulation model, and found it to better reflect the underlying neural relationship dynamics than earlier, correlation based methods of estimating connectivity.

Some of these earlier methods of estimating connectivity employed the technique of cutting the time series for different conditions, which causes loss in important task related variations at the block boundaries (Buchel, 2004). An alternate strategy uses interaction (Buchel and Friston, 1997), such as in PPI, the method used in the present study (Friston et al., 1997). This approach therefore models block designed fMRI tasks more efficiently with less data loss than earlier methods (Buchel, 2004).

Dynamic Causal Modeling (DCM) is a newer method that combines the deconvolution step of PPI with estimation of effective connectivity, modeling the interaction between nodes at the neuronal level, which is converted to hemodynamic

response function time-series at each node (Friston et al 2003). This allows a more biologically feasible model, although this advantage is more important in event related designs, compared to block designs (Buchel, 2004).

Another advantage of PPI is that it is a model free whole brain analysis method, which might be particularly advantageous for investigating connectivity in neuropsychiatric disorders, as it might be challenging to define an appropriate a-priori model in such cases.

## 7.8 Interpreting the Findings from the Present Study at a Systems Level

The results of the present study showed disconnectivity from the amygdala to several brain regions, for socio-emotional function. As discussed in detail in Chapter one, the amygdala is believed to play a pivotal role in social and emotional function. It is associated with functions including detecting the emotional or social salience of an input stimulus (Pessoa and Adolphs 2010), especially when related to fear and threat, and accordingly modifying cognitive processing and behavioral output (Adolphs, 2001, Phelps and LeDoux, 2005, Anderson, 2007, Phillips et al., 2001) or emotional learning (Gallagher and Holland 1994, Morrison and Salzman 2010, Ludmer et al., 2011, Holland and Gallagher 2004, Morris et al., 1996, Suslow et al., 2006), both in cases of incidental and intentional perception, and in conscious and unconscious processing (Hall et al., 2004, Marco et al., 2005, Stein et al., 2007) and finally for facial emotion recognition in humans (Adolphs, 2001, Adolphs, Tranel and Damasio, 1998). Also human patients with amygdala damage demonstrate impaired experience of fear in response to threatening external stimuli (Feinstein et al., 2011).

Relevant to connectivity, the amygdala is believed to be a key hub in socio-emotional networks (LeDoux, 1996, Allman and Brothers, 1994, Stein et al., 2007, Marco et al., 2005). The amygdala receives direct and indirect inputs from various sensory regions, connects to the hippocampus, and also projects to motor regions such as lateral thalamus and periaqueductal grey (LeDoux, 2003, Amaral, 1992, LeDoux 1987). Other regions such as the temporal polar cortex and perirhinal cortex are also bi-directionally connected to it. Additionally, the amygdala is also connected to cortical regions including the anterior cingulate cortex and orbitofrontal cortex

(Krolak-Salmon 2004, Holland and Gallagher 2004). Many of these connections have also been found to be abnormal in schizophrenia (as reviewed in Benes, 2010).

Further, some of the regions that the results of the present study show to have reduced connectivity to the amygdala are themselves believed to be major connectivity hubs. Network simulation studies have found that lesions in the TPJ are more disruptive to overall connectivity in models, compared to other regions (Alstott et al., 2009), which implies this is an important connectivity hub. Additionally, the precuneus was also shown in a whole brain functional connectivity studies to be a major connectivity hub (Tomasi et al., 2010, Tomasi et al., 2011). Further, white matter abnormalities have also been reported for these regions in schizophrenia (Antonius et al., 2011). Therefore the disconnectivity shown in the present study might have critical effects on eventual socio-emotional function, mediating some of the socio-emotional behaviour abnormalities seen in the disorder.

At a systems level, a top-down model of contextual regulation of instantaneous emotion is proposed by some (Reichenberg and Harvey, 2007), with temporal regions such as the amygdala and frontal regions such as the medial prefrontal cortex playing affective and cognitive roles respectively (Ochsner and Gross, 2008, Fakra et al., 2008, Ochsner et al., 2002). As per this model, reduced connectivity might induce deficits in this regulatory mechanism, manifesting abnormal activation patterns to cope with smaller cognitive loading, and possibly failure under higher cognitive loading. This also agrees with the hypo-frontality often reported in schizophrenia, as well as the fact that such over-activation is not universally found in all studies of the disorder (Hill et al., 2004).

Further, such variance in emotional regulation is also seen in health. Not only are individual differences seen in response to stress and emotion, these capacities vary based on the nature of the emotion and social environment. This might reflect similar tendencies as seen in patients in healthy individuals with a genetic disposal to schizophrenia, which might in interaction with other genetic and environmental factors manifest as disease features. Neural plasticity markers such as BDNF impact function of these socio-affective networks, probably by mediating activity-dependent modifications in networks (Castren et al., 2007). This could mediate individual differences in vulnerability to stress or psychiatric disorders (Alleva and Francia, 2009).

## 7.9 Limitations Associated with Functional Connectivity

Investigating the connections between different parts of the brain is an important part of understanding brain function. Connectivity, however, has been defined at many levels, such as anatomical and functional. Traditionally anatomical connectivity was measured using dyes and tracers which cross the synaptic cleft followed by histological techniques (Yeterian and Pandya, 1994). Such methods are applicable in non-human primates, and post-mortem studies. Today methods such as diffusion tensor imaging are used to investigate anatomic connectivity, which estimates white matter tracts by measuring the highly anisotropic direction of water diffusion within such fibers. Functional connectivity describes "temporal correlations between spatially remote neuro-physiological events" (Friston et al., 1993). Various functional neuroimaging methods, particularly EEG, PET and fMRI, have been used to investigate functional connectivity. The concepts and history behind functional and effective connectivity have been described in detail in the introduction (see section 1.4.2) as well as above (see section 7.4). In this section we discuss the limitations of functional connectivity.

Firstly, functional connectivity describes statistical correlation between activity in separate brain regions, two collections of neurons, or neuron-like circuits, based on the idea that 'activities that covary together suggest that the neurons generating the activities may be interacting' (Horwitz et al., 2005). It does not presume anatomic connections, because the same behaviour could be produced by neurons connecting in different ways (Horwitz, 2003). In particular PPI analysis between-groups relates to group difference between the 'regression coefficient obtained from regressing the activity at any point in the brain on the activity of the

seed region, or change in activity per unit change in the seed region' (Friston, 2011). Two sample t-test on this regression coefficients tests the null hypothesis that there is no group difference in coupling. Therefore, this is similar to a comparison of correlations with the seed region (Friston, 2011). Therefore the relevance of structural versus functional investigation for understanding of brain function has been questioned (Lee et al., 2003).

Indirect connections, or connections between two regions mediated by a third region, might incorrectly appear as direct influences unless these mediating regions are accounted for in the model (Goebel et al., 2003). Therefore functional connectivity, or functional coupling, might be found between two regions in the absence of any direct connection between them, or two directly connected regions might not be connected functionally.

A limitation of fMRI based functional connectivity is the temporal and spatial loss of information associated with fMRI, which is an indirect method of estimating neuronal activity by measuring haemodynamic data. There is a temporal difference in haemodynamic and neural activity: the temporal sampling rate for fMRI (in the order of seconds) is spare compared to the timing of neural events (in the order of milli-seconds). Additionally, there is a spatial loss of information as multiple neurons could correspond to a single voxel.

Another key limitation of functional connectivity is that the neurobiological basis is not completely understood (Horwitz, 2003, Horwitz et al., 2005). It describes "patterns of neural activity", rather than "explanations of their origins" (Lee et al., 2003). In fact recent studies have suggested that the BOLD response is closer to local field potentials than multi-unit responses, and therefore BOLD response might relate

to synaptic processes more than neuronal firing (Logothetis et al., 2001). Further, both excitatory and inhibitory synaptic activity increase might lead to increased metabolic activity (Horwitz et al., 2005, Logothetis, 2003). How the observed BOLD fMRI signal relates to the underlying neural activity, and how biological factors such as CSF and heart-rate interact with these measurements and functional connectivity is also unclear (Heeger and Ress, 2002, Logothetis, 2008, Maldijan, 2001, Rogers et al., 2007). Functional connectivity has been shown to vary with task load (Rowe et al., 2002) as well as with physiological factors such as cardiac and respiratory factors (Birn et al., 2006, Bhattacharyya et al., 2004). It has been shown to be impacted by drugs (Li et al., 2000) and antipsychotic medication via synaptic plasticity (Stephan et al., 2001). For these reasons it has also been criticized as an 'elusive concept' (Horwitz, 2003), as the physical basis is not clear.

However, functional connectivity methods have been extensively applied, as well as several studies have attempted to validate them and elucidate their neurobiological basis. One study examining correlations in low frequency fluctuations in the inter-hemispheric auditory cortex compared between a subject with callosal agenesis and a healthy subject demonstrated reduced functional connectivity, in validation of functional connectivity (Lowe et al., 1997). Other studies have used neural models to validate and investigate the basis of functional connectivity (for review, see Horwitz, 2004). Specifically for functional connectivity using PPI, Kim and Horwitz investigated neuro-biological validity using simulated neural activities and fMRI signals generated by a large-scale neural model. They reported that the PPI-based functional connectivity results generally agreed with the nature of the underlying neural interactions (Kim and Horwitz, 2008). Stein et al investigated

effective connectivity in combination with known anatomical connectivity for macaque data (Stein et al., 2007). Moreover, animal studies have combined microstimulation and fMRI to investigate network connections and provide further validation of these methods (Logothetis, 2003, Field et al., 2008, Matsui et al., 2011). Additionally, resting state functional connectivity has been combined with structural connectivity (Venkataraman et al., 2011, Kim et al., 2011). Structural connectivity has also been used to constrain, or provide priors for, effective connectivity analysis (for review see Stephan et al., 2009). Such strategies combining multiple methods might model brain function more accurately, as well as further elucidate the neuro-biological basis of functional connectivity (Friston, 2011).

In summary, although there are extensive plausible reports of functional connectivity, as well several studies which attempt to validate these methods, we do not completely understand it's biological basis. Therefore the specific methods and assumptions used should always be considered alongwith results from studies of functional connectivity.

## 7.10 Limitations of the Investigating the BDNF Val66Met SNP in Relation to Schizophrenia

In the present study I have investigated the effects of variation in the BDNF val66met SNP on effective connectivity for fear and approachability processing. The reasons for choosing this choice SNP were threefold, as discussed earlier. Firstly, BDNF is strongly associated with plasticity, which in turn has been linked to effective connectivity. Secondly, BDNF has been linked to fear related learning and social learning, particularly for learning from aversive social encounters. Finally, BDNF val66met SNP has been associated with schizophrenia. There are some important caveats of examining a single SNP in BDNF, the val66met SNP, in connection with schizophrenia, which are discussed in this section.

Schizophrenia has a polygenic etiology, with multiple genetic factors interacting with each other (Harrison and Weinberger, 2005, Lang et al., 2005, Keshavan et al., 2008, Sun et al., 2008), as well as environmental factors (Lawrie et al., 2008, Tsuang et al., 2000, Benes et al., 1997, Palomo et al., 2004) to affect disease manifestation. Thus understanding the susceptibility introduced by one SNP with schizophrenia is complex, and understanding individual SNPs affects endophenotypes for schizophrenia has been suggested instead (Ho et al., 2006, Casey et al., 2010).

Further, BDNF has also been associated with various factors such as age (Katoh-Semba et al., 1997), gender (Verhagen et al., 2010, Foltynie et al., 2005), ethnicity (Pivac et al., 2009) and environmental factors such as psycho-social stress (Smith et al., 1995), which might further complicate the understanding of how it impacts brain function (Chao et al., 2008, Angelucci et al., 2005, Angelucci et al., 2000, Bai et al., 2003, Grillo et al., 2007, Xu et al., 2010, Chen and Huang, 2011).

Although the association between the BDNF val66met SNP and schizophrenia has been extensively investigated (Jindal et al., 2010, Egan and Weinberger 1997, Hall et al., 2007, Lu and Martinowich, 2008, Muglia et al., 2002, Le Strat et al., 2009, Rybakowski 2008, Angelucci et al., 2005, Shoval and Weizman, 2005), the results are heterogenous. Some studies linked the val allele with higher risk (Neves-Pereira et al., 2005, Rosa et al., 2006, Golimbet et al., 2008, Rizos et al., 2009) and some found no association (Tochigi et al., 2006, Jonsson et al., 2006, Watanabe et al., 2006, Yi et al., 2011, Chang et al., 2009). Interestingly, because BDNF has also been linked to ethnicity (Pivac et al., 2009), a meta-analysis of all related studies in Asian populations found no association between val66met and schizophrenia (Naoe et al., 2007), whereas many of the studies showing positive associations are Caucasian. Neves-Pereira et al studied a Scottish population that included 321 probands for schizophrenia, 263 probands for bipolar affective disorder, and 350 controls and found highly significant association of the val allele with schizophrenia but not bipolar disorder. Haplotype analysis of val66met SNP and a dinucleotide repeat polymorphism in the promoter region showed that the methionine haplotype was significantly under-represented amongst the schizophrenic, but not the bipolar population, suggesting the risk associated with val66met may depend upon haplotypic background (Neves-Pereira et al., 2005). However, Tochigi et al found no association between val66met and schizophrenia in a study with 401 patients with schizophrenia and 569 controls (Tochigi et al., 2006). Therefore the association between schizophrenia and val66met is not clear.

Further, these associations are likely to be mediated by complex cellular and molecular mechanisms of BDNF, which are not fully understood (see Lu and

Martinowich, 2008, and Buckley et al., 2011 for detailed review). The BDNF protein exists in two forms in the brain, pro and mature. It has an activity dependant as well as spontaneous component. The BDNF gene has a complex expression, varying with both brain region as well as stage of development (Lu and Martinowich, 2008). Multiple promoters and mRNA transcripts are associated with BDNF, distributed in different regions, different cell types and different parts of the cell. BDNF expression is mediated by intracellular Ca2+, and is impacted by neuronal activity (West et al., 2001). This transcription can be differentially regulated by several physiological stimuli (Lu and Martinowich, 2008). Further, brain and peripheral levels of BDNF are also reduced in schizophrenia (for review see Green et al., 2011). How these mechanisms might impact upon plasticity or functional connectivity in schizophrenia is not clear.

It has been suggested that the val66met SNP might be linked to slower plasticity changes (in the order of days to weeks), whereas the plasticity changes related to functional connectivity are faster (in the order of milliseconds and seconds). Further, these changes might apply inside individual cells, and are more local (Lu, 2003). Therefore the spatial and temporal considerations for functional and effective connectivity discussed in the previous section might further complicate the effect of val66met on functional and effective connectivity, which is a key feature of schizophrenia (Peled, 2005).

In conclusion, some of the limitations for investigating the association between the BDNF val66met and schizophrenia have been discussed here, and these limitations should considered alongwith the results.

## 7.11 Limitations of the Methods used in the Present Study

In this section I have discussed a few limitations of the present study. Firstly, in the present study I have examined a specific type of effective connectivity, using PPI, which indicates the change in influence of a neuronal system over another, for a change psychological context, but does not indicate if this relationship is causal (Friston, 1994, Friston et al., 1997). Additionally, I have not investigated any related structural connectivity.

Secondly, there might be a possible influence of antipsychotic medication in patients on synaptic plasticity (Stephan et al., 2001), although no evidence was found of a correlation between effective connectivity in this study with medication dose. Further, although the findings in the present study are statistically robust, and the population sizes are good for fMRI studies, the size of patient population did not allow an investigation of the effect of genetic variation amongst patients. Also symptom correlations might be even more insightful in future studies with larger populations sizes.

Thirdly, the findings in the present study could be improved by taking into account factors including more specific behavioural measures corresponding to event related task performance within scanner (for example, measures of how the subjects rated each face), as well as state and trait anxiety measures for BDNF, to investigate the correlation of the functional network abnormalities shown here with behaviour. These issues might be addressed in future investigations.

## 7.12 Future Work Leading from the Present Study

In the present study, the population sizes did not permit examination of genetic effects in patients. These associations are further complicated by interaction between factors including medication and age of onset in patients, with synaptic plasticity, as discussed above. Therefore an important future direction might be to examine the effect of genetic variation on these functional networks amongst individuals with schizophrenia. Other genes, such as NRG-1, associated with both schizophrenia and plasticity might be investigated.

As discussed earlier, factors including structural connectivity and synaptic plasticity and neurotransmitters contribute to connectivity. Future work might employ multimodal imaging to examine multiple factors for connectivity together (including techniques such as diffusion weighted imaging, diffusion tensor imaging, arterial spin labelling and spectroscopy).

At present to our best knowledge this is the only study which has examined connectivity for social judgement in schizophrenia. Due to the prominence of abnormalities in social behaviour in schizophrenia, this is an interesting avenue for future research. Investigations of connectivity for several aspects of social judgement in schizophrenia might further aid understanding of how these behavioural deficits are mediated. Due to limitations of population size, more than one study using similar paradigms and replicating the same result might prove worthwhile. Importantly, due to the complex presentation of schizophrenia, it might be valuable for future work large populations to include correlation of abnormalities in functional networks with symptom presentation.

Additionally, within healthy individuals, investigation of individual variation in socio-emotional function, as well as contextual modulation of emotion and social behaviour, corresponding to variation in personality and genes, as well as environmental factors such as socio-emotional stress might lead to deeper understanding of how the networks for social behaviour and emotional processing function in health. Gene association studies are beginning to explore how multiple genetic variations impacts neural basis for traits. Due to the intrinsic effect of several genetic factors on connectivity, and the modulation of their action by environmental factors, as well as epistasis with other genes, extending these examinations to connectivity might be an exciting new avenue of research.

## 7.13 Conclusion

The majority of individuals afflicted with schizophrenia continue to suffer from their hallucinations and other symptoms indefinitely. As discussed in the introduction, schizophrenia is hard to characterise, and despite much progress in research on this subject, many aspects of the disorder remain unclear. Therefore each scientific finding regarding schizophrenia might be a valuable addition to our understanding of the disorder.

A plausible unifying theory of schizophrenia, the disconnection hypotheses, proposes that disconnectivity is a core pathological feature of schizophrenia. Abnormalities in social behaviour and emotional processing play a prominent role in the disorder, and both these categories of mental functions are sub-served by a well characterised distributed network of brain regions. Although several studies have shown disconnectivity in schizophrenia, particularly for emotion processing and facial affect recognition, to our best knowledge this has not been investigated for social judgment based on facial affect. Further, schizophrenia is highly heritable, and some of these genetic factors also intrinsically impact upon connectivity. Nevertheless, despite several studies showing abnormal connectivity for these genetic factors, it is not clear how their effect on disease features, such as abnormal socio-emotional function, are mediated. Further, the task of comparing and consolidating the findings from existing studies faces the challenge of varying methodological details.

In the present study I have shown disconnectivity in schizophrenia for the first time during a social judgement task, as well as during emotional processing, using common procedural details, such as method of estimating connectivity, seed region

and image acquisition and processing parameters, as well as partially overlapping subject populations. Further, I show a similar pattern of disconnection in individuals carrying the met allele of the BDNF val66met SNP. Thus I provide results in keeping with the hypotheses of the present study. These hypotheses included abnormal connectivity in patients with schizophrenia in the psychological context of an emotion processing task involving fearful faces, as well as a social cognition based approachability judgment task. Additionally the hypothesis of the present study also included an association between the BDNF val66met SNP, which also modulates synaptic plasticity, and thereby connectivity. Specifically, the hypothesis stated that there would be significant connectivity variation associated with the BDNF gene on the same two psychological tasks of fear processing and approachability judgment. The results of the study again support these hypotheses. Therefore here I have presented specific manifestations of disconnection in schizophrenia, which is likely to be a core physiological feature of the disorder.

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# Appendix

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| 0.006 | 706 | 5.12 | 58, -64, 8 | Middle temporal gyrus |
| < 0.001 | 1277 | 4.55 | 34, -72, -16 | Right fusiform gyrus |
| < 0.001 | 1500 | 4.47 | -36, -76, -20 | Left cerebellum |

**Table 1 Fear Processing in Healthy Participants**

This table shows the regions with significantly overactivated for the fear versus neutral contrast, at 0.005 threshold, uncorrected, in healthy participants.

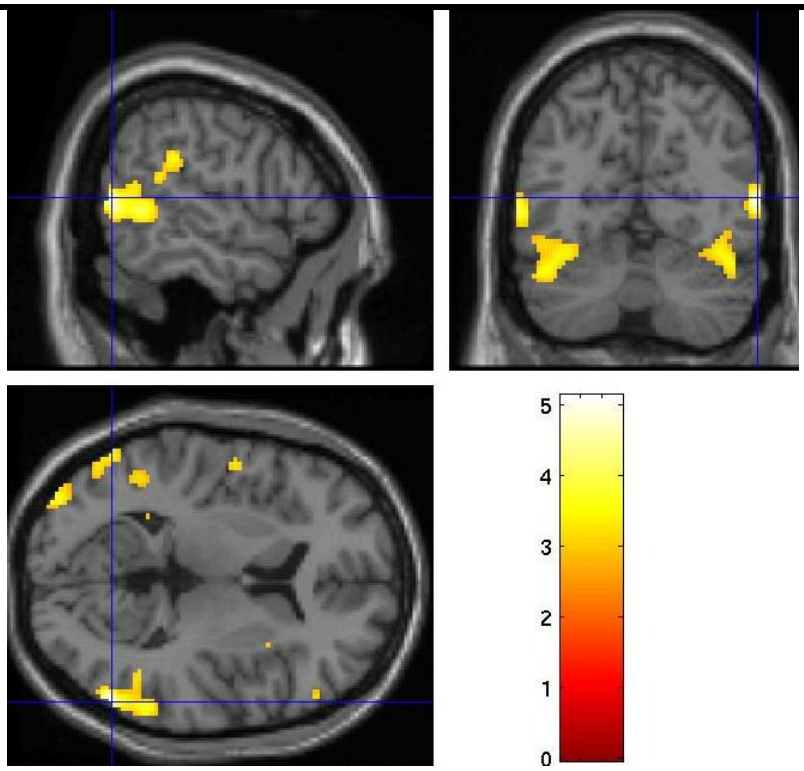


**Figure 1 Fear Processing in Healthy Participants**

This figure is a SPM illustrating the regions significantly overactivated for the fear versus neutral contrast in healthy controls in yellow, at a threshold of $p < 0.005$, uncorrected, in healthy participants. Cross hairs are at MNI coordinates 58, -64, 8

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| < 0.001 | 2652 | 5.57 | -8, 40, 52 | Left Superior Frontal Gyrus |
| < 0.001 | 1660 | 5.30 | -28, -90, -34 | Left fusiform gyrus |
| 0.007 | 978 | 4.69 | 56, 24, 0 | Right inferior frontal gyrus |
| 0.007 | 994 | 4.27 | 30, -88, -36 | Right fusiform gyrus |
| 0.001 | 1290 | 4.55 | -52, 18, -10 | Left superior temporal gyrus |
| 0.029 | 23 | 3.96 | 18, 2, -18 | Right Amygdala (Using SVC) |
| 0.035 | 17 | 0.035 | -22, -8, -20 | Left Amygdala (Using SVC) |

**Table 2 Approachability Judgement in Healthy Participants**

This table shows the regions with significantly increased activation in approachability versus gender contrast, at $p < 0.005$ threshold, uncorrected

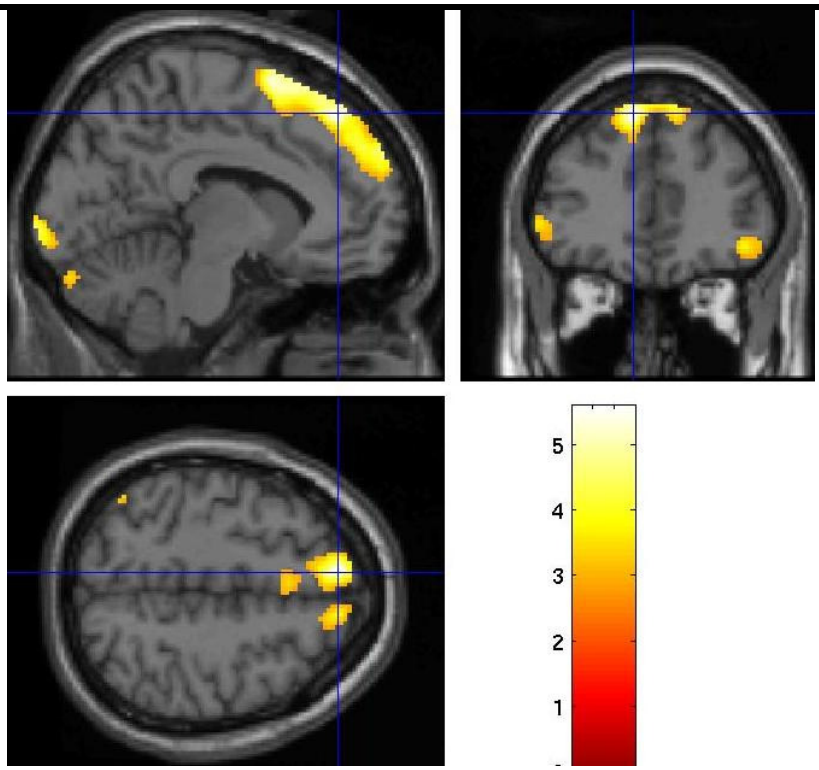


**Figure 2 Approachability Judgement in Healthy Participants**

This figure is a SPM illustrating the regions with significantly increased activation in approachability versus gender contrast, at $p < 0.005$, uncorrected threshold, in yellow. The cross hairs at MNI coordinates -8, 40, 52

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| < 0.001 | 1108 | 5.76 | -36, -54, -14 | left fusiform gyrus |
| 0.001 | 887 | 4.62 | 40, -56, -24 | right fusiform gyrus |

**Table 3 Left Amygdala Connectivity for Healthy Controls**

This table shows the connectivity from the left amygdala, for the approachability versus gender contrast, for controls, at p < 0.005 threshold, uncorrected

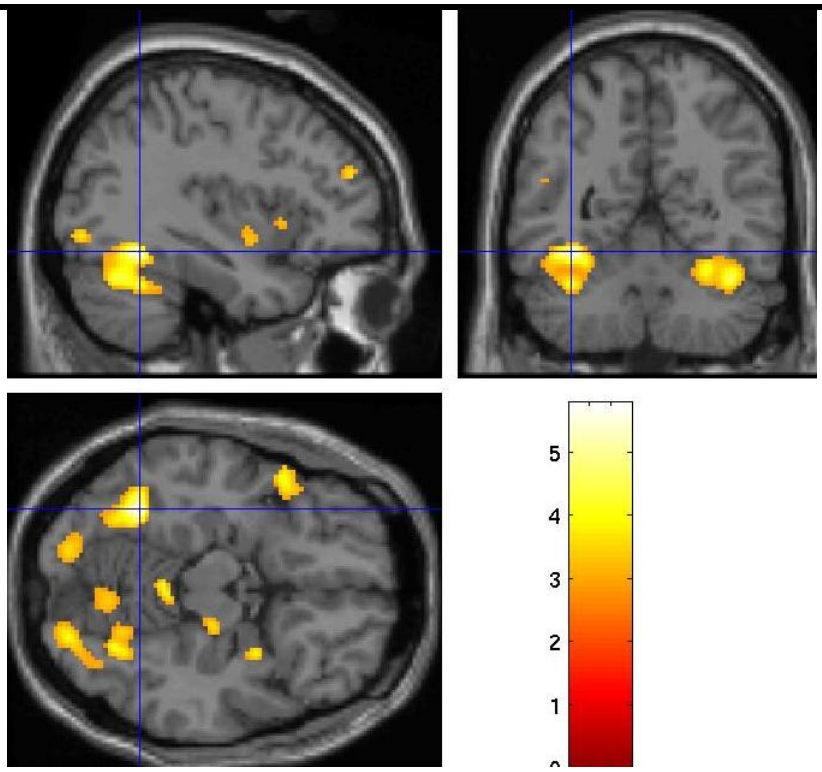


**Figure 3 Left Amygdala Connectivity in Healthy Controls**

This figure is a SPM illustrating the connectivity from the left amygdala, for the approachability versus gender contrast, for healthy controls, at p < 0.005 threshold, uncorrected, in yellow. The cross hairs at MNI coordinates -36, -54, -14

| $P_{corr}$ | $K_E$ | T | x,y,z (mm) | Region of Peak Activation |
|---|---|---|---|---|
| < 0.001 | 1413 | 6.33 | -16, -96, 0 | left fusiform gyrus |
| 0.046 | 424 | 4.07 | -16, 34, 52 | superior frontal gyrus |
| < 0.001 | 2250 | 6.11 | 32, -46, -26 | right inferior occipital gyrus |

**Table 4 Right Amygdala Connectivity in Healthy Controls**

This table shows the effective connectivity from the right amygdala, for the approachability versus gender contrast, for controls, at $p < 0.005$ threshold, uncorrected

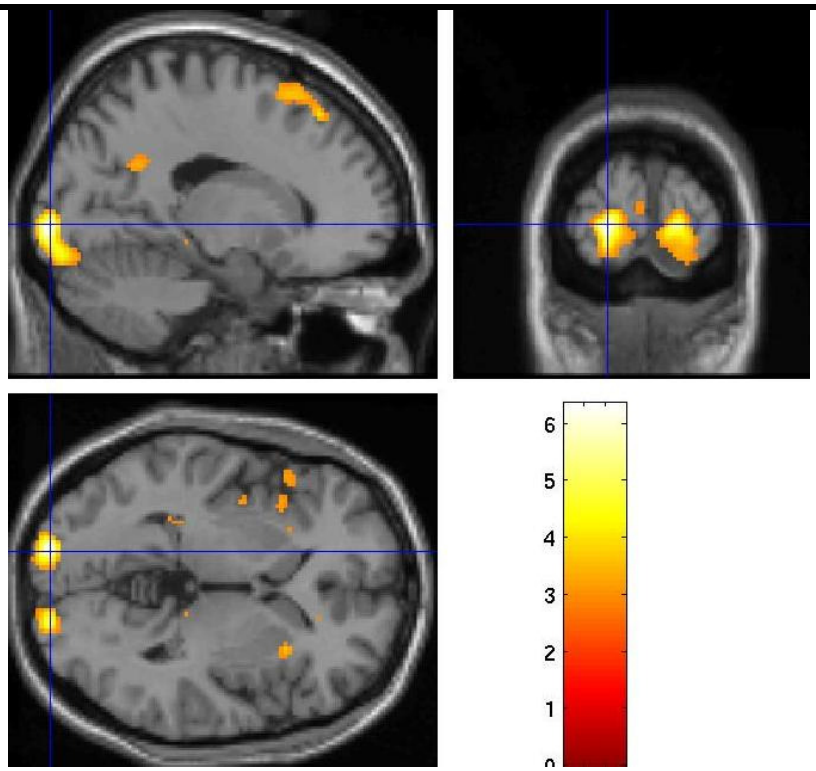


**Figure 4 Right Amygdala Connectivity in Healthy Controls**

This figure is a SPM illustrating the connectivity from the right amygdala, for the approachability versus gender contrast, in yellow, for controls, at $p < 0.005$ threshold, uncorrected. The cross hairs at MNI coordinates -16, -96, 0

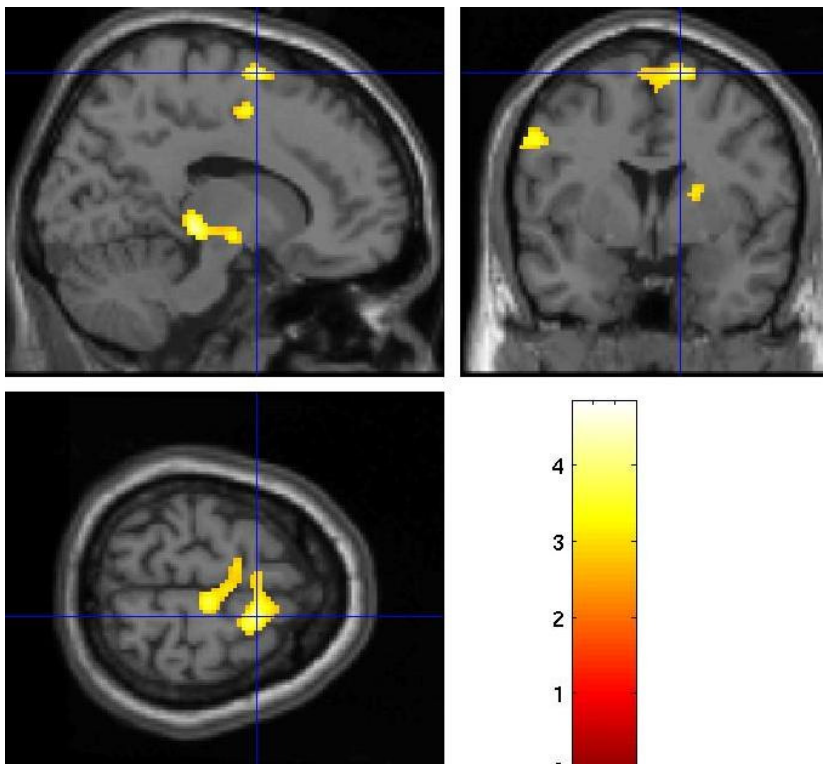


**Figure 5 Reduced Connectivity for Approachability versus Gender Judgement in Met Carriers from Left Amygdala**

This figure is a SPM illustrating additional brain regions with significantly lower effective connectivity, from the left amygdala, corresponding to the approachability versus gender contrast, at threshold 0.005, uncorrected, in met allele carriers as compared to the val homozygotes (val-val > val-met + met-met). Regions with significantly decreased connectivity are in yellow. Extent threshold 500 voxels. Cross hairs at 14, 2, 68.

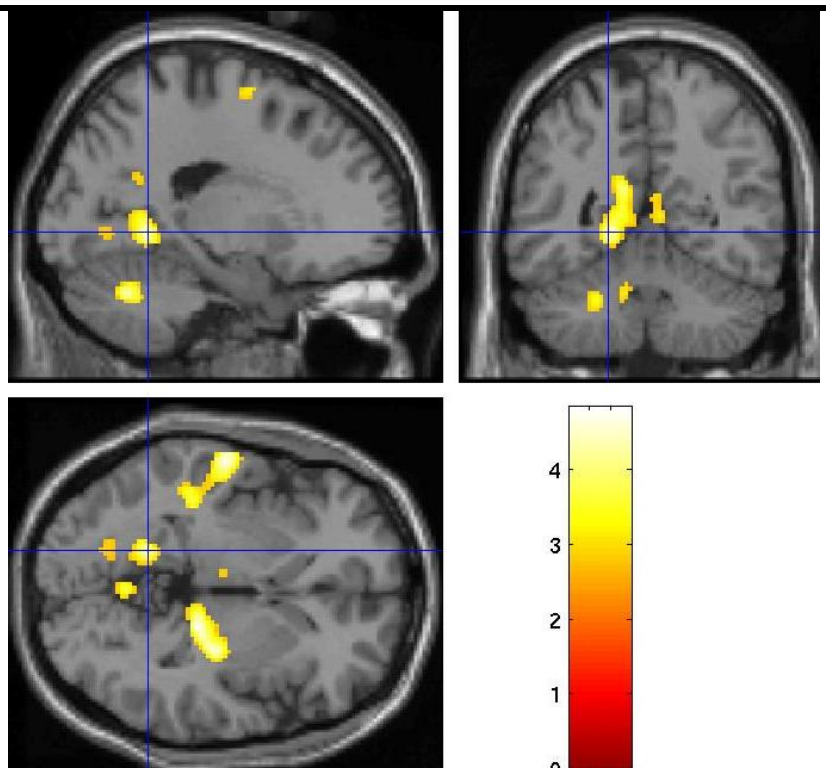


**Figure 6 Reduced Connectivity for Approachability versus Gender Judgement in Met Carriers from Left Amygdala**

This figure is a SPM illustrating additional brain regions with significantly lower effective connectivity, from the left amygdala, corresponding to the approachability versus gender contrast, at threshold 0.005, uncorrected, in met allele carriers as compared to the val homozygotes (val-val > val-met + met-met). Regions with significantly decreased connectivity are in yellow. Extent threshold 500 voxels. Cross hairs at -18 -52 -2.

## Publications Related to the Present Project

At the time of writing this thesis, the following papers have been prepared for submission to journals:

- Mukherjee et al., (2011): "Effects of the BDNF Val66Met polymorphism on neural responses to facial emotion." Psychiatry Research Neuroimaging, 191(3):182-8.

- Mukherjee et al., (2011) "Lower Effective Connectivity between Amygdala and Temporo-Parietal Junction in Response to Fear Faces found in Schizophrenia.", 'Schizophrenia Research' In Press.

- Mukherjee et al., (2011) "Fronto-Temporal Connectivity during Approachability Judgement in Schizophrenia.", in progress.