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Neural Correlates of Cognitive and Emotional Processing in Individuals At-risk for Schizophrenia and First episode Psychosis

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Heline Mirzakhanian

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2010
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San Diego State University

2010

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DEDICATION:

I dedicate this manuscript to my parents, Heghoosh and Edvard, who have forgone their own aspirations to provide a better future for their children. You have always supported me, and have never doubted my dreams and endeavors, no matter how crazy they might be. Thank you for being there at every crossroad in my life; it is your strength that has made me who I am today.
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ABSTRACT OF DISSERTATION

Neural Correlates of Cognitive and Emotional Processing in Individuals At-risk for Schizophrenia and First Episode Psychosis

by

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San Diego State University, 2010
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Efforts to prevent or lessen the functional impact of the onset of schizophrenia can be informed by a better understanding of brain systems involved in cognitive and emotional processing at the earliest stages of the disorder. Yet, studies investigating these early stages of schizophrenia are rare. A fuller understanding of disruptions in the neural systems underlying cognitive and emotional processing at these earliest stages of psychosis will lead to more targeted efforts to prevent or minimize functional limitations among patients with psychosis.

Using functional magnetic resonance imaging (fMRI), the present study compared brain functioning associated with emotional as well as cognitive processes in groups of individuals who exhibited early and sub-threshold symptoms of psychosis to patients
(P/AR) in their early phases of psychosis and/or immediately after their first psychotic episode (FE) and to healthy individuals (HC). We also explored to what extent the engagement of neural systems during these challenges is related to or predicted by individual emotional and cognitive performance as well as global functioning along the psychosis spectrum.

Contrary to our expectations, load-related brain activation during the working memory challenge was similar among all three groups in a region of DLPFC that was task-responsive across the groups, although whole-brain analysis revealed group differences in other regions. Amygdalar brain activation during the emotional challenge, in contrast to our hypothesis, was not different between the HC and P/AR groups and was increased in magnitude in the FE group. Neuropsychological performance was related to DLPFC brain activation in both FE and P/AR groups, but in opposite directions. We also found associations between global functioning and magnitude of brain response during the emotional and cognitive challenges.

The present results suggest that both cognitive and emotional systems are implicated in the earliest stages of psychosis. Further analyses suggested that brain responses were associated with neuropsychological performance as well as overall global functioning scores. Our findings highlight that more basic neurobiological abnormalities likely account for overall global functioning early in the course of schizophrenia. Our results could be interpreted as supporting a dysregulation hypothesis of developing psychosis such that global functioning is compromised as a function of disruption in the regulatory mechanisms between cognitive and emotional systems.
INTRODUCTION

Disabling Functional Impairments in Schizophrenia are Linked to Cognitive and Emotional Deficits

Functional deterioration is a hallmark of schizophrenia. Patients with schizophrenia commonly have impairments in global functioning across several domains, including, establishing and maintaining interpersonal relationships and employment, poor social adjustment as well as deficits in many domains of independent living. In 2002 the economic impact of schizophrenia was estimated to be $62.7 billion (Wu et al., 2005). A recent study suggested that this burden is even greater within the first few years after the onset of the disorder (Nicholl et al., 2010). The etiology of functional impairment is likely multi-factorial and possibly several factors contribute to the emergence and progression of deterioration. The onset of schizophrenia early in life, during late adolescence, is likely one contributor. Late adolescence or early adulthood is an important period for the development of personal and social skills necessary for establishing interpersonal relationships, instituting a personal identity and developing adaptive skills for conflict management. The development of these skills is disrupted in young adults who suffer from schizophrenia. In addition, the nature of the symptoms present in schizophrenia lead to further isolation and stigma. Furthermore, the majority of patients with schizophrenia have neuropsychological deficits that almost invariably lead to poor functional outcome in schizophrenia (Green et al., 1996). Specifically, it appears that there is an association between verbal memory abilities and executive functioning including working memory and novel problem solving and functional outcome (e.g.,
functioning at school, work or interpersonal relationships) (Green et al., 2000a&b).

Interestingly, contrary to a more intuitive belief that functional outcome might be closely related to positive psychotic symptoms such as hallucinations, research has shown that negative affective symptoms are more strongly associated with deficits in functional outcome and cognition (Green et al., 2000a&b; Bowie et al., 2006). Thus, it appears that both cognitive and emotional factors play a role in creating and maintaining deficits in functioning among patients with schizophrenia. Indeed, it seems likely that a failure of proper integration of cognition and emotion to produce healthy emotional behavior is a crucial area of deficit in poorly functioning patients with schizophrenia.

Better Understanding of Cognitive and Emotional Deficits at the Earliest Stages of Schizophrenia May Lead to Better Preventative or Rehabilitative Interventions

A large body of evidence has accumulated demonstrating that patients with schizophrenia have deficits in basic cognitive and emotional processes. Abnormalities in human face perception and emotion identification for example have been repeatedly reported (Kohler, et al., 2003 & 2006) and these in conjunction with widespread neuropsychological deficits likely result in disrupted emotional behavior that in turn impacts global functioning. Studies looking closely at the pathophysiology and neural correlates of schizophrenia and the aforementioned deficits are conclusive about the presence of structural and functional brain abnormalities in schizophrenia underlying these basic cognitive and emotional processing deficits. Recently, there has been increasing interest in developing interventions to improve functional outcome among
patients with schizophrenia. The recovery movement, for example, emphasizes that change in functioning is possible and focuses on empowering individuals with schizophrenia to break out of a view of lifelong disability (Peebles et al., 2007). In addition, there is a growing interest in developing prevention programs for at-risk individuals that will reduce the functional impact of schizophrenia (Woods et al., 2003; McGlashan et al., 2006; McGorry et al., 2002; Morrison et al., 2004). However, in order to design the most effective prevention and rehabilitation programs, the first step in the process should be to understand the basic cognitive and emotional abnormalities in schizophrenia and how they may interact to contribute to functional limitations. A full understanding will involve investigating the behavioral and neurophysiological underpinnings of cognitive and emotional deficits and their integration. Even more powerful is the idea of understanding at what stage in the development of the illness these brain changes occur and how these are similar or different in people who are at risk for the illness.

**Cognitive and Emotional Brain Systems Interact in Healthy Individuals to Produce Emotional Behavior**

Human emotional behavior is complex and it is facilitated by several neural systems in the brain underlying both emotion perception as well as emotional behavior execution to emotional cues. Specifically, emotional behavior appears to be dependent upon two neural systems, a ventral system and a dorsal system (Hariri, Bookheimer & Mazziotta, 2000; Phillips, et al., 2003a). Findings suggest that the ventral system
including amygdala and insula, is significant for identification of affective states whereas the dorsal system including the dorsolateral prefrontal cortex (DLPFC), is important for executive function including effortful cognitive regulation of affective states and decisions about execution of behavior. The integrity of both systems independently, but also as a network, is important for healthy emotion processing and emotional behavior. Disruptions at any stage of this network can impact aspects of human behavior and may lead to pathology (Phillips et al., 2003b).

Evidence for Abnormalities of Cognitive (Dorsal) and Emotional (Ventral) Brain Systems in Schizophrenia

Abnormalities in both systems have been repeatedly reported in schizophrenia and the presence of cognitive and emotional/affective processing deficits in schizophrenia is well established (Gur, Keshavan & Lawrie, 2007; Ragland et al., 2007). Against a background of more generalized cognitive deficits, numerous studies have suggested that patients with schizophrenia show profound deficits in memory and executive functioning such as deficits in attention, working memory and verbal learning (Heaton et al., 2001; Green et al., 2002; Dickinson et al., 2004; Brown et al., 2007). These neurocognitive deficits are considered to be central to the pathophysiology of schizophrenia. Numerous studies for example have reported working memory deficits in schizophrenia across different cognitive paradigms (Park & Holzman, 1992; Gold et al., 1997; Teck et al., 2002; Kim et al., 2004). It appears that both components of working memory, the maintenance and central executive, are impaired in schizophrenia (Kim et al., 2004).
Neuroimaging studies of patients with schizophrenia consistently show abnormal brain activation patterns in regions within the dorsal prefrontal cortex related to these working memory and executive deficits. Generally, functional imaging studies of schizophrenia suggest hypoactivation of prefrontal cortex function during cognitive challenges (Andreasen et al., 1997; Carter et al., 1998, Haznedar et al, 1997; Eyler et al., 2002). A large number of studies have specifically investigated functional activation to working memory tasks in schizophrenia (Ragland et al., 1998; Callicott et al., 2000; Perlstein et al., 2001; Ramsey et al., 2002; Jansma et al., 2004; Cannon et al, 2005). Whereas some studies have reported a DLPFC deactivation in schizophrenia (Carter et al., 1998; Andreasen et al., 1997; Cannon et al., 2005) others have reported hyperactivation in similar regions reflecting inefficiency (Callicott et al., 2003). It appears that working memory load has moderating effects on brain activation and some suggest that the relationship of brain activation and working memory demands progress in an inverted U-shape fashion. While patients with schizophrenia show overactivation with increasing memory load, they are unable to sustain activation at high levels for longer periods resulting in a non-linear relationship between brain activation and working memory load (Callicott et al., 2003; Manoach et al., 2000). This pattern is also observed in healthy populations but it is suggested that patient groups reach capacity (the peak of the inverted U) earlier than healthy individuals and hence when patients are compared with healthy individuals, patients show hyperactivation at lower working memory loads (Manoach et al., 2000). This inverted U-shape has not always been observed, however, even in studies that parametrically varied load (Cannon et al, 2005). Functional
abnormalities are in accord with structural neuroimaging findings that suggest structural brain changes in temporal and frontal volumes in schizophrenia (Wright et al., 2000; Shenton et al., 2001; Zhou et al. 2003; DeLisi et al., 2004; Whitworth et al., 2005).

Impairments in emotion identification and regulation as well as deficits in social functioning are also well established in individuals with schizophrenia and seem to be related to brain abnormalities in the ventral system (Morrison et al., 1988; Mandal et al., 1998; Green et al., 2000a). It appears that some deficits are linked to defective identification and reaction to facial affect. Kohler and colleagues (2003) for example evaluated recognition of range of emotions and neutral expressions in patients with schizophrenia and reported that compared to healthy individuals the patient group demonstrated impairment in overall emotion recognition. Using the facial affect computer task (FACT) Edwards and colleagues (2001) compared facial affect identification in a group of patients with schizophrenia to patients with other psychotic disorders, affective psychosis patients and healthy controls and found that although all patient groups demonstrated deficits compared to healthy individuals in facial affect recognition and discrimination, patients with schizophrenia performed poorest. Interestingly, no group differences were apparent between the groups in emotion labeling. Findings suggest that among other neuropsychological deficits (e.g., impairment in visual imagery) facial affect identification is associated with impairments in executive dysfunction (Whittaker, Deakin & Tomenson, 2001). Furthermore, patients with schizophrenia often misinterpret social cues. For example, basic social interactions between two individuals may be misperceived by many patients with schizophrenia as
threatening to self triggering or maintaining persecutory delusions. Phillips, Senior &
David (2000) suggested that schizophrenia patients with persecutory delusions appear to
have specific abnormalities in viewing strategies for ambiguous social scenes perceiving
ambiguous stimuli as more threatening. In addition to the relationship between cognitive
deficits and affect processing there also appears to be a strong association between social
outcome and ability to accurately recognize emotions of others (Green et al., 2000b).
Findings suggest that specific abnormalities in identification of emotionally salient
material, together with misinterpretations of intentions and impaired regulation of
resulting beliefs and emotional behavior may underlie some symptoms and poor social
outcome in patients with schizophrenia (Kohler et al., 2000; Bruene, 2005). The inability
to recognize mental states from eye expressions (Kington et al., 2000) or gaze, for
example, has been interpreted as an inability of many patients with schizophrenia to infer
and attribute mental states to others as well as to explain and predict behavior (Premack
& Woodruff, 1978).

Neuroimaging studies of patients performing emotional tasks have shown
dysfunction of the limbic system, particularly in the amygdala, as compared to healthy
volunteers (Schneider et al., 1998; Taylor et al., 2002). These reports usually demonstrate
a failure to activate the amygdala in the patient group to a level seen in healthy controls
(Phillips et al., 1999). When comparing neural response to facial expression in paranoid
schizophrenia patients, non-paranoid schizophrenia patients and healthy control, Phillips
and associates (1999) found that the patient group had overall less amygdalar activation
and lower accuracy in identification of facial expressions. In addition, the authors found a
differential activation pattern within the patient group suggesting that the paranoid schizophrenia patients were more accurate in recognizing expressions, and demonstrated greater amygdalar activation than non-paranoid patients. A subsequent study (Williams et al., 2004) reported that reductions in amygdala activity were associated with excessive arousal responses in paranoid schizophrenia patients suggesting a specific disjunction of arousal and amygdala-prefrontal circuits leading to deficits in processing of threat-related stimuli. The authors further argue that this dysregulation in the cycle or feedback loop between amygdala and autonomic activity can lead to misattributions and hypervigilance associated with paranoia. Patients with schizophrenia showed similar hypoactivation relative to healthy individuals in response to a task requiring discrimination of positive from negative facial affect valence consistent with reports of greater involvement of the left amygdala in evaluative aspects of emotion processing (Gur et al., 2002a). Some authors have also related this lack of limbic activation to an over-activation of the prefrontal cortex and suggested that this pattern not only attests to the limbic dysfunction in schizophrenia but also reveals a compensatory role for the prefrontal cortex during emotion processing. Structural imaging studies in individuals with schizophrenia also suggest reduced amygdalar, hippocampal and parahippocampal volumes (Kasai et al., 2002; Steen et al., 2006).

Thus, there is strong behavioral and neuroimaging evidence that adults with chronic schizophrenia show abnormalities in emotional behavior that are related to basic deficits in emotional and cognitive processing in ventral and dorsal systems within the brain.
Moving Back from the Middle of the Developmental Spectrum:

The majority of studies in the past several decades have focused on chronic patients with schizophrenia. Thus, there is proportionally more knowledge and advancement in the scientific and health care community about the symptoms, neural processes, social ramifications and treatment applications of individuals with chronic schizophrenia who are in their 40s than there is knowledge about the course of schizophrenia in late life or very early and in its prodromal stages. The prodromal stage in schizophrenia can occur up to 5 years prior the onset of full psychotic symptoms. The prodrome is characterized by mild cognitive, affective and behavioral symptoms and signs that gradually worsen during progression of disease (McGlashan & Johannessen, 1996). There is also a decline in functioning and nonspecific signs such as social withdrawal.

The study of schizophrenia early in its development or even before the onset of psychosis has several advantages. One obvious advantage is that understanding the disease and its triggers early on will likely lead to early treatment and potentially to intervention and better functional outcome. In fact, there is research suggesting that duration of untreated psychosis is negatively associated with symptom severity and functioning (McGlashan & Johannessen, 1996) and medication efficacy (Crow et al., 1986; Scully et al., 1997). In addition, the onset of psychosis is thought to be associated with a rapid sharp decline in cognitive abilities as well as structural brain changes that could be potentially ameliorated by early intervention (Pantelis et al., 2003; DeKoenig et al. 2009). From a purely methodological perspective, conducting research early in the
disease course can potentially minimize confounding variables that among other issues hinder conclusions about cause and effect relationship or etiology. Schizophrenia, especially in its chronic stages is associated with substance abuse and other comorbid conditions (Buckley et al., 2009). Similarly, it is difficult for researchers to disentangle disease specific changes, for example in brain blood flow, from long-term medication effects or side-effects (Harrison, 1999). Finally, understanding the disease early on can increase our understanding of the disease as it progresses. Thus, it seems that an integral part of research in schizophrenia should include the study of individuals at risk for schizophrenia or patients during their first-episode of psychosis. Although research in the schizophrenia prodrome is still in its infancy, several interesting behavioral, cognitive and emotional parallels have been noted between individuals at-risk for schizophrenia and chronic patients with schizophrenia (Cornblatt et al., 2003). In addition, several structural and functional changes associated with schizophrenia appear to predate the onset of the illness and have been found in prodromal individuals and individuals with familial genetic risk (Pantelis et al., 2007; Fusar-Poli et al, 2007). Even more interestingly, several recent studies have found a relationship between cognitive deficits and functional disability even in at-risk individuals (Niedman et al., 2006; Shim et al., 2008; Monte et al., 2008).

**Behavioral, Cognitive and Emotional Changes Along the Psychosis Spectrum**

Several studies have shown that schizophrenia even in its prodromal period is marked by cognitive decline and emotional impairments (Hawkins et al., 2004; Keefe et
al., 2006; Eastvold et al. 2007; Jahshan et al., 2010). Similarly, deficits have been repeatedly observed in association with genetic vulnerability or risk for schizophrenia. For example, first-degree relatives of individuals with schizophrenia are at an increased risk for developing schizophrenia or a schizophrenia spectrum disorder but not other psychiatric disorders (Kendler & Diehl, 1993). The prodromal period in schizophrenia is marked by the gradual development of low-grade psychiatric symptoms and signs, including reduced concentration and attention, anergia, depressed mood, sleep disturbance, anxiety, social withdrawal, suspiciousness, deterioration in role functioning, and irritability (McGlashan & Johannessen, 1996, White, Anjum & Schulz, 2006). Progression of prodromal phase leads to the emergence of some attenuated psychotic symptoms such as thought and perception disturbances as well as disorganized thinking and speech. If further progression occurs then these sub-threshold symptoms are followed by more intermittent, transient but severe psychotic symptoms including hallucinations and delusional thinking that may eventually evolve into a ‘full-blown’ psychosis marking an individuals first psychotic episode. (Yung & McGorry, 1996; Davidson et al., 1999). In view of this evidence the study of individuals with sub-threshold symptoms (prodromal) as well individuals genetically at-risk for psychosis seems appropriate. Specifically, although attenuated behavioral symptoms that are observed in the prodromal phase of schizophrenia are at times observed in relatives of patients, most at-risk individuals do not display behavioral manifestations to the extent observed in the prodromal stage (Lee et al., 2008). Nevertheless, both groups show cognitive and emotional deficits at basic neural structural and functional levels (Fusar-Poli et al., 2007).
The neurodevelopmental model suggests that such deficits even precede the emergence of psychosis and are also present in genetically at-risk individuals (Cannon et al., 2003). Working memory deficits, for example, have been evidenced in high risk adolescents and non-psychotic relatives of schizophrenia patients (Wood et al., 2003). Furthermore, there appears to be a linear progression in magnitude of neurocognitive deficits across different stages of the psychotic spectrum. Compared to healthy individuals prodromal or at risk individuals perform worse on neurocognitive measures, but they perform better when compared to first-episode psychotic patients (Eastvold, Heaton & Cadenhead, 2007). More importantly, in a preliminary analysis of neurocognitive performance within the prodromal group alone, Eastvold and colleagues (2007) reported a dissociation in prodromal individuals, with those who converted performing more poorly on test of verbal memory and general intelligence than those who did not convert. Recent studies investigating affect in high risk populations are suggestive of abnormalities in facial affect recognition in these individuals (Habel et al., 2004, Phillips & Seidman, 2008). Similar to cognitive deficits, affective processing deficits appear to be biological risk markers for schizophrenia. Numerous studies using neuroimaging methods have found brain correlates to the cognitive and emotion processing deficits described above (Fusar-Poli et al., 2007).

**Brain Correlates of Emotional and Cognitive Processing Deficits In Prodromal and First-Episode Schizophrenia:**
Neuroimaging studies in prodromal schizophrenia are rare, although a handful of studies have examined adults at genetic risk for schizophrenia and first-episode patients. There is some evidence suggesting that structural brain abnormalities are present in high risk individuals (Cannon et al., 1998; Keshavan et al., 1997, 2002) while others disagree (McDonald et al., 2002; Sharma et al., 1998; Staal et al., 1998; Seidman et al., 1999, 2002). Overall, amygdalar and hippocampal complex volume reductions are most consistently reported in both at risk individuals and first-episode psychotic patients, with the latter group showing the most volumetric reductions (O’Driscoll et al., 2001; Seidman et al., 1999, 2002; van Erp et al., 2002; Keshavan et al., 2002; Lawrie et al., 1999, 2001). Overall, findings of brain structure abnormalities in at risk and prodromal individuals are less conclusive while there are more robust findings in first episode patients.

Functional imaging studies in high risk populations and first episode schizophrenia patients are also limited, and there have been no published studies using individuals who are prodromal for schizophrenia. Similar to the results from chronic patients reviewed above, there are conflicting findings about the directionality of frontal lobe activation abnormalities (i.e., hyper- vs. hypoactivation) among studies of at-risk groups and first episode psychosis patients. Several studies revealed hypofrontality in relatives and offspring of patients with schizophrenia relative to healthy controls after matching the groups on task performance (Keshavan et al., 2002; O’Driscoll et al., 1999). In contrast, other studies of working memory related brain activation in relatives of schizophrenia patients have predominantly reported hyperactivation in the right DLPFC (Brahmbhatt et al., 2006; Callicott et al., 2003; Seidman et al., 2006; Theremenos et al.,
2004). As in the chronic schizophrenia literature, load and performance levels may explain some of these discrepancies. A recent study by Delawalla and colleagues (2008) comparing siblings of individuals with schizophrenia to healthy controls during an attentional working memory task reported task-related hyperactivation in several brain regions including the DLPFC during a short delay condition (low demand) but hypoactivation during the long delay (high demand) condition. The authors concluded that the pattern observed in the siblings of patients represents an inverted U-shape relationship between activation and task demand that lies between that of healthy individuals and patients. Similarly, a study by Karlsgodt and associates (2007) investigated brain activation and performance during a verbal working memory challenge in schizophrenia patients, unaffected twins and controls and found that unaffected twins of schizophrenia patients showed a brain-performance relationship intermediate to patients and controls in DLPFC and parietal cortex. Results of studies of brain activation during cognitive tasks in first-episode psychotic patients appear to be somewhat more consistent. Overall, several studies have found hypo-activation during tasks of working memory, executive function, planning, attention and context processing (Tan et al., 2005; Mendreck et al., 2005; Riehemann et al., 20001; Snitz et al., 2005; Rasser et al., 2005; Morey et al., 2005; MacDonald III et al., 2005). Tan and colleagues (2005) for example, investigated both maintenance and manipulation of working memory in first-episode patients relative to healthy controls and reported a deactivation in DLPFC. They also found, however, increased activation in the VLPFC that they interpreted as a compensatory response to the hypoactivation in more dorsal regions. Similarly,
Riehemann and associates (2001) reported hypofrontality in unmedicated first-episode patients in response to a task of cognitive flexibility and category switching that was not present in healthy individuals. In another study by Mendrek and colleagues (2004), first episode psychosis patients demonstrated greater DLPFC activation during an easy condition but hypoactivation during a more demanding condition. Studies of emotional processing in prodromal or first episode patients are even more limited. A recent review (Phillips & Seidman, 2008) reported that individuals clinically at risk for psychosis show differences in brain activation associated with processing of emotional and more pronounced neutral facial expressions despite an adequate behavioral performance.

Another study by Habel and colleagues (2004) investigated amygdalar activation in non-psychotic brothers of schizophrenia patients during a mood induced emotional paradigm. Consistent with findings in the chronic schizophrenia population, they found that compared to controls the at-risk siblings demonstrated decreased amygdalar activation.

Finally, using a facial matching task, identical to the task we propose in the present study, Fakra and associates (2008) found that first-episode schizophrenia patients failed to activate regions of the limbic system including the amygdala. Furthermore, the authors reported an inverse functional connectivity between frontal regions and the left amygdala in healthy individuals but not in the patient group (Fakra et al., 2008).

In general, findings in neuroimaging, albeit somewhat inconclusive, highlight that at-risk individuals and first-episode psychotic patients display abnormalities in brain functioning in similar brain regions observed in more chronic schizophrenia patients. In
addition to aberrant executive systems, deficient brain activation patterns in emotional systems seem also to predate the onset of psychosis and these remain present in early psychosis. No study to date has used functional neuroimaging in prodromal individuals, however, and none has looked at both cognitive and emotional processing and brain function within the same group. It remains to be shown how these two processes that are supported by different but integrated neural systems function in the same individual. This is particularly important when considering how individual differences in neural response to cognitive and emotional tasks may relate to more general deficiencies in emotional behavior and functioning.

Cognitive and Affective Heterogeneity Argue for Examining Neural Correlates of Individual Differences

Although, as previously described, most patients with schizophrenia have some level of dysfunction, there is evidence of a subgroup of chronic schizophrenia patients who appear to be neuropsychologically normal (Palmer et al., 1997). There is also a wide range of affective and emotional impairment in schizophrenia. While some patients have more negative symptoms and impairment in social interaction others report less negative symptoms (Stahl & Buckley, 2007). This heterogeneity is also reflected in prodromal stages and first episode psychosis with some patients presenting with more affective psychotic symptoms such as mood symptoms and impulsivity whereas others display less affect dependent psychotic symptoms (Haroun et al. 2006). This heterogeneity is of special interest when considering its potential diagnostic value. For example, while some
individuals may progress to develop schizophrenia others may develop other disorders in the schizophrenia spectrum such as schizoaffective disorder or even bipolar disorder (Haroun et al. 2006). As reviewed above, individual differences in cognition and affect also appear to be related to level of functioning and outcome. Thus, in addition to comparing brain response of prodromal and first episode patients to that of healthy individuals, it is also important to understand how brain response relates to other measures of cognition, emotional behavior, and functioning among the patient groups.

Summary and Rationale for the Present Study

Functional impairment in schizophrenia appears to be related to both cognitive and affective deficits that lead to impaired emotional behavior. As described above, one of the main neuropsychological impairments in schizophrenia is executive dysfunction including working memory deficits. Working memory deficits can account for many of the cognitive abnormalities in schizophrenia. The inability to temporarily hold and manipulate thoughts for example can result in disorganized thinking or speech often observed in schizophrenia (Daban et al., 2003). In conjunction with deficient affective identification of stimuli these working memory deficits can result in many other symptoms observed in schizophrenia such as inappropriate affect and more importantly negative symptoms such as flat affect that in turn lead to inefficient social skills and maladaptive global social functioning (Fiszdon & Johannesen, 2010). While research has identified the link between cognitive deficits and schizophrenia liability and psychosis, few studies (Becerril & Barch, 2010; Cohen et al., 2006) have looked at both cognitive
and emotional processing in both groups. Even fewer studies (e.g., Pauly et al., 2009) have used neuroimaging methodology to investigate the functional brain response to a cognitive and emotional challenge across these groups. Furthermore, there has been little attempt to examine the severity and nature of neurobiological abnormalities in emotion and cognition together at the earliest stages of psychosis. Thus, several interesting questions have remained unanswered when studying correlates of executive function and emotion processing across the psychosis spectrum. For instance, 1) when in the course or spectrum of psychosis do executive and emotion identification/matching deficits occur? 2) Does one deficit precede the other? That is, is there an interaction between developmental stage and a specific deficit? 3) Are deficits in one task associated with those on the other task within each group and across groups? 4) How do individual affective and neurocognitive differences on these specific tasks contribute to more general abnormality? Finally, which deficit as measured by brain abnormality is predictive of global functioning? Thus, in this study we investigated both cognitive and emotional systems involved in emotional behavior with the aim to shed some light on emotional behavior and its brain correlates along the schizophrenia spectrum. In addition to obtaining knowledge about neural mechanisms implicated in at risk or prodromal individuals and those with first-episode schizophrenia, we hope that these preliminary findings could serve as basis for future studies. Of particular interest would be longitudinal studies following high risk and first episode groups over an extended period of time examining conversion rates, medication effects and the utility of neuroimaging as a diagnostic and prognostic tool. We hope that the present study will serve as an initial
step in helping to elucidate the complex and likely interactive nature of cognitive and emotional processes, their neural correlates and their association to global functioning in schizophrenia.

**Aims**

**Aim 1:** To understand the contributions of risk of schizophrenia and experience of a first psychotic episode on neural systems involved in basic cognitive and emotional processes putatively related to deficient emotional behavior and functioning.

**Hypothesis 1a:** We hypothesized differences in the magnitude of brain activation in regions of the DLPFC across the three different groups during a cognitive verbal working memory challenge. Specifically, based on previous findings using a spatial working memory challenge (Cannon et al., 2005) we hypothesized that healthy individuals would show greater activation in the DLPFC during the maintenance of verbal items (as measured by a linear increase in brain response with number of items to be maintained) when compared to prodromal/at risk individuals. Furthermore, we predicted that prodromal/at risk individuals would show greater activation in the DLPFC during the maintenance condition of the verbal working memory task when compared to the first episode individuals.

**Hypothesis 1b:** Similarly, we hypothesized differences in the magnitude of brain activation in the amygdala across the three different groups during an emotional face
matching challenge. Specifically, we hypothesized that amygdalar brain response during the emotion matching condition compared to a sensorimotor control condition would be greater in healthy controls compared to prodromal/at risk individuals. Furthermore, we predicted that prodromal/at risk individuals would show greater activation in the amygdala during the emotion matching condition compared to a sensorimotor control condition when compared to the first episode individuals.

**Aim 2: To explore to what extent the abnormal engagement of neural systems during cognitive and emotional challenge is related to or predicted by individual emotional and cognitive performance as well as global functioning in prodromal/at-risk and first-episode patients.**

**Hypothesis 2a:** We hypothesized that individual cognitive functioning as measured by neuropsychological performance will be associated with brain activation response in the at-risk and first episode patients in areas of abnormal DLPFC response during the verbal working memory challenge.

**Hypothesis 2b:** We hypothesized that individual accuracy scores during an emotion identification task will be positively associated with brain activation in the amygdala in at-risk and first episode patients during the emotion matching task.

**Hypothesis 2c:** We hypothesized that levels of emotional distress and sleep disturbance, as potential indicators of a more affective versus non-affective psychosis profile, would
be associated with brain activation in the amygdala in at–risk and first episode patients during the emotion matching task.

**Hypothesis 2d:** We hypothesized that individual global functioning as measured by a composite score of functioning will be associated with brain activation response in the at–risk and first episode patients in task-related regions of the DLPFC during the verbal working memory challenge as well as with brain activation in the amygdala at–risk and first episode patients during the emotion matching task.
METHODS

Participants

A total of 38 individuals participated in the study. Data from four individuals were excluded due to high levels of head motion when undergoing imaging. Thus, a total of 34 participants successfully completed the study. Specifically, there were 10 individuals in the prodromal / at risk group (P/AR), 12 participants in the first episode (FE) group, and 12 participants in the healthy control (HC) group. Participants were assigned to the P/AR group if they met criteria for low grade symptoms, attenuated positive symptoms or a family history of schizophrenia or schizotypal personality disorder in a first degree relative in conjunction with a change in mental state or functioning. Specifically, low grade symptoms and attenuated positive prodromal symptoms were measured using the Structured Interview for Prodromal Symptoms (SIPS) and individuals scoring a “3” or higher on the psychotic items of the SIPS, indicating moderately severe symptoms, were considered to be in the attenuated symptom prodromal group or at risk. Individuals with a first degree relative with psychosis or a diagnosis of schizotypal personality disorder plus a change in mental state or decline in functioning as measured by the Global Assessment of Functioning (GAF) scale (Hall, 1995) for a duration of at least one month were considered in the genetic risk and deterioration prodromal group. Nine of the ten participants had low-grade or attenuated positive symptoms and one had a family history plus deterioration. These two subgroups were combined for the present study into a single prodromal / at risk group. Individuals who had experienced their first psychotic episode per the SCID within the last two years
were included in the FE group. The inclusion of first episode subjects allowed comparison of brain response between those who have already experienced a psychotic episode and those who are at risk, or have converted since initial study participation. A comparison group of normal participants were matched with the experimental groups according to age, sex, education, socioeconomic and marital status. Individuals with a history of an Axis I or Axis II mental disorder, or serious medical or neurological illness were excluded.

Demographic Characteristics:

All three groups were similar in age, years of education and marital status (Table 1). The control group included an equal ratio of female to male participants while there were more male participants in the other two groups (Pearson chi square = 6.0, df = 2, p = .05). We investigated potential interaction effects of gender with brain activation, behavioral performance and other variables of interest and did not find any significant interaction effects with other relationships of interest (see Results section). Within the overall sample, 44.1% of the participants were Caucasian, 21.6% Hispanic, 17.6% African American, 8.8% Asian Indian, 5.9% Asian and 2.9% Pacific Islander. There were no differences in ethnicity distribution across the groups. All but two participants were English language dominant and no statistically significant differences were found across the groups when examining language dominance.

All potential participants were evaluated for their eligibility to safely undergo an
MRI and anyone with metallic implants (such as pacemakers or bone pins) was not allowed to participate in this study as this is a contraindication for MRI. Participants were asked during screening if they have any metal in their body, and a questionnaire was completed prior to fMRI asking about past surgeries and metallic implants. Further, women who were lactating or pregnant were excluded to avoid any potential unknown risks to fetuses or nursing infants. These criteria resulted in the exclusion of three potential participants from the study.

Participants over the age of 18 years were asked to give informed consent. We asked participants below the age of 18 years to provide assent and asked their guardian to sign a consent form for study participation.

Reruitment

Potential participants were recruited from a pool of individuals who had already participated in the study entitled, “Vulnerability Markers in Prodromal Schizophrenia” conducted by Dr. Cadenhead. Recruitment efforts at the Cognitive Assessment and Risk Evaluation (CARE) program included explaining the study procedure to interested individuals. Of the 54 individuals approached to participate, 38 individuals were eligible and agreed to participate. Participants were compensated for time and travel ($35).
Measures

Diagnostic, mood, sleep, neuropsychological, and emotion processing assessment

As part of their assessment at the CARE program, participants completed several diagnostic and functional scales including the Structured Clinical Interview for DSM-IV (SCID) or Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS), Structured Interview for Prodromal Syndromes (SIPS), and Brief Psychiatric Rating Scale (BPRS)(First et al., 1997; Kaufmann et al., 1997; McGlashan, 2001; Overall & Gorham, 1962).

Individuals who qualified to participate in the fMRI study also completed the Beck Depression Inventory-2 (BDI-2) or its youth version, the Beck Anxiety Inventory (BAI) or its youth version and the Pittsburgh Sleep Quality Index-monthly (PSQI) (Beck et al., 1996; Beck et al, 1988; Buysse et al., 1989). The PSQI is a standardized self-rated questionnaire developed to assist in measuring global sleep quality. The 24-item questionnaire generates seven component scores, with subscale scores ranging from 0 to 3: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. The sum of these seven components yields a global score of subjective sleep quality. The global score ranges from 0 to 21, and a higher score is indicative of poorer subjective sleep quality. A score of > 5 identifies clinically significant sleep disturbance with 89.6% sensitivity and 86.5% specificity (Buysse et al., 1989).

As part of their neuropsychological assessment at the CARE program, participants completed measures of executive functioning (Wisconsin Card Sorting Test,
WCST and Stroop Color and Word Test, SCWT), processing speed (Numerical Attention and SCWT and Color Naming), verbal memory (Hopkins Verbal Learning Test-Revised, HVLT), working memory (Wechsler Adult Intelligence Scale-Letter-Number Sequencing, WAIS-3 and Wechsler Memory Scale-Spatial Span, WMS-3) and general intelligence measures (WAIS-3 and Wechsler Intelligence Scale for Children, WISC-3) (Table 1) (Heaton et al., 1993; Golden, 1978; Benedict and Zgaljardic, 1998; Wechsler, 1997b; Wechsler, 1991).

Prior to participation in the magnetic resonance imaging scan, participants completed an emotion identification task (Arce et al., 2009). Tasks similar to this have been previously used in studies of social cognition and schizophrenia and demonstrated deficits in facial affect processing in schizophrenia as described above (Edwards et al., 2001). Previous studies however have predominantly used static pictures of faces as stimuli. The task used in our study is different in that the presented human faces are not static pictures but the stimuli are dynamic and changing facial displays. The dynamic nature of the task, that is the integration of motion, is thought to facilitate perception of emotional faces (Ambadar et al., 2005). In addition, this task appears to be more ecologically valid and approximating ‘real-life’ as emotion processing often occurs in an interactive and dynamic context. During this task, which was completed outside of the scanner, participants were shown dynamic faces that morphed from a neutral condition to an emotionally loaded condition (e.g., happy or angry). Participants were asked to choose the identified emotion as quickly as possible. As a baseline condition to control for general psychomotor speed and processing of morphed images, participants identified
morphing shapes on the screen. Duration of the task was approximately eight minutes. This task was used to test predictions about the specific emotional processing components that are impaired in individuals prodromal for schizophrenia or in their first episode.

Imaging tasks:

Working memory task: We used an adapted version of the Sternberg verbal working memory task created by Karlsgodt and associates (2007) emphasizing the maintenance of verbal information across short periods of time. This specific task (Karlsgodt et al., 2007) and tasks of this type have been successfully implemented in previous neuroimaging studies in schizophrenia and have yielded activation in the dorsolateral prefrontal cortex (DLPFC) related to increasing working memory load (Callicott, et al., 1999; O’Hare et al., 2008). This increasing involvement of the frontal central executive aspect of working memory with increasing load is thought to reflect the limited capacity of the posterior working memory buffer. That is, once the simple mnemonic capacity of a posterior memory buffer is exceeded, frontally mediated strategic processes must be invoked in order to maintain and retrieve information from the buffer (Cannon et al., 2005). In schizophrenia, the structure and functioning of the DLPFC is thought to be differentially disturbed against a background of more generalized dysfunction, leading to specific behavioral impairments in working memory capacity. This adapted version of the Sternberg task was created by Cannon and associates for assessing the capacity of the verbal working memory system. While in the scanner the participant was asked to study an array of stimuli consisting of lowercase letters. Stimuli
were presented for 2 seconds. After a delay of 4 seconds, an uppercase probe letter appeared, and the participant was asked to press the response key indicating whether he or she believed the probe matched one of the targets. The participant was given 2 seconds to make this choice. Experimentally, the load placed on working memory processing was changed by varying the number of letters to be maintained (e.g., loads of 3, 5, 7, or 9 letters).

_________________________ Insert Figure 1 Here______________________________

Emotion-Face Matching Task: The Emotion-Face Matching Task is frequently used in neuroimaging studies examining emotion matching in healthy individuals and has also been used in the study of psychiatric patients (Hariri et al., 2002 & 2005). Several studies have repeatedly shown significant amygdalar activation in response to this paradigm (Altshuler et al., 2005; Hariri et al., 2003; Paulus et al., 2005; Meyer-Lindenberg et al., 2006; Wang et al., 2004; Wright et al., 2006), and one study showed amygdala deficits among first-episode patients with schizophrenia (Fakra et al., 2008). While in the scanner, participants were presented with a target face (on the top of the screen) and two probe faces (on the bottom of the screen) and were instructed to match the probe with the same emotional expression. A block consisted of six consecutive trials where the target face is either angry, fearful, or happy (Ekman et al 1983). Each trial lasts 5 seconds. During sensorimotor control blocks, participants were presented with 5-second trials of ovals or circles in an analogous configuration and instructed to match the shape of the probe to the target. Each run consisted of 3 blocks of angry, 3 blocks of fearful, 3 blocks of happy stimuli, and 3 blocks of sensorimotor control trials.
Scanning Procedure:

All structural and functional MRI data were obtained from the 3T GE magnet at the Keck Center on the UCSD campus. The overall duration of scanning was 60 minutes.

Structural Scans:

A high-resolution structural sequence was acquired for anatomical reference. The MPRAGE image was collected in the sagittal plane (Flip angle = 8, Band Width =31.25, FOV = 240, Slice thickness = 3mm, in-plane resolution 1.875x1.875 mm, 170 slices, 1.00 NEX), which took nine minutes. We also collected a Diffusion Tensor Imaging scan for future analyses not to be included in this study.

Functional Scans: A total of three functional scans were acquired, measuring blood oxygen level dependent (BOLD) brain response during facial emotion matching and working memory. For 24 out of the 34 successful participants, we acquired two runs of the facial emotion matching task to increase the signal strength. The Emotion Face Recognition Task was acquired using the following parameters: TR = 2000, TE = 32ms, Flip angle = 90, FOV = 23, Slice thickness = 2.6mm, 1.4mm gap, 30 slices, matrix = 64 X 64, Bandwidth = 250 (ramped) with 290 brain images collected. The other functional scan was a Verbal Working Memory Task. This task required 256 repetitions, TR = 3 s,
TE = 45 ms, flip angle = 90°, FOV = 200, and 33 3-mm-thick interleaved slices (with 1 mm gap) acquired parallel to the intercommissural plane in a 64 x 64 matrix covering the whole brain.

Data Analysis:

Demographic, Clinical, and Cognitive Performance Measures: We used univariate ANOVAs to compare groups for any measure in which all three groups were tested, and then conducted follow-up t-tests to make pairwise comparisons for any measures with a significant group effect.

Emotion Processing Task and Behavioral Data from Brain Challenge Tasks: Both the Emotion Processing Task and the Emotion Matching task given in the scanner had 3 emotion conditions and a shape condition. The Verbal Working Memory task had 4 load conditions. All tasks had measures of both reaction time and accuracy. Separately for reaction time and accuracy, we used an ANOVA to examine the main effects of Group and Condition and the interaction of Group and Condition. We then conducted ANOVAs for each condition separately to examine the effect of Group. When the Group effect was significant, follow-up t-tests were used to make pairwise comparisons between the three groups.

Individual subject processing: Neuroimaging data were analyzed using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). Data were corrected for possible motion artifacts and four individuals with excessive head
movement (i.e., visually-identifiable movements on greater than 30% of the time points) were excluded from further analysis (2 HC, 1 FE and 1 P/AR). Slice timing correction was applied, and manual registration of the functional data to the anatomical images was conducted for each task. For each participant, the general linear model was used to examine task-related brain response. For the verbal working memory task, there were two contrasts of interest: all working memory loads compared to baseline, used to identify a task-related region of interest across the three groups within which load-related effects could be compared between groups, and the linear effect of load (9>7>5>3) which was used to examine group differences in a whole-brain exploratory analysis. For the emotion matching task, the contrast of interest was the difference between response during emotion matching for each emotion separately compared to that during sensorimotor control trials. These contrast terms were entered into the model predicting each task’s brain response, along with a baseline (intercept) term, a linear trend term, and the movement parameters from the motion correction algorithm. Maps of the fit coefficient for the contrasts of interest were created for each subject and these maps were blurred with a 6mm FWH Gaussian filter for both the VWM cognitive challenge and for whole brain analyses of the Emotion Face Matching task. No blurring was applied for amygdala region of interest analyses of the Emotion Face Matching task due to the small size of the structure. For analysis of the verbal working memory data, and for exploratory whole brain analyses, the maps were then normalized to Talairach coordinates. For those participants with two runs of the Emotion Face Matching task, the processed data from the two runs were averaged and the average was used for group analyses.
Group Analyses:

Hypothesis 1a:

To compare the magnitude of brain activation in task-related DLPFC regions across the three different groups during the cognitive verbal working memory challenge, we conducted voxel-wise analyses within the DLPFC to create a region of interest in which to examine load-related effects. For the purposes of this study, the DLPFC was defined by the Talairach Daemon (Lancaster et al., 2000) bilateral middle frontal gyrus region. At each voxel in DLPFC, we used single sample t-tests to identify voxels that were significantly activated (p<0.01) and that clustered together into a region whose volume was at least 1024 mm$^3$ (16 contiguous voxels). This protected a DLPFC-wide probability of false positive cluster detection of p<0.05. We created two such maps within the DLPFC, one for the control group and one for the combined experimental group (P/AR and FE together). A conjunction of these two maps yielded a single task-related region of interest (ROI; Figure 2). Within this region of interest we conducted our main analyses examining the linear load effects. Specifically, we used ANOVA to look for main effects of Group and Load and Group x Load interactions. Then we used an ANOVA at each load separately to look for Group effects and conducted follow-up t-tests to examine the nature of observed effects (pairwise comparisons between groups).

________________Insert Figure 3 Here______________________________

________________Insert Figure 4 Here______________________________
**Hypothesis 1b:**

To compare the magnitude of brain activation in the amygdala across the three different groups during an emotional face matching challenge we restricted our analysis specifically to the amygdalar region as our region of interest (ROI). We used the AFNI program DrawDataset which uses information from the Talairach Daemon software (Lancaster, 2000) to obtain region of interests (ROIs) of the left and right amygdala in each individual. The mean value of the fit coefficient for the contrast between emotion matching and the sensorimotor control condition was computed across all the voxels in the ROI in each individual’s native space. We first used an ANOVA to look for main effects of Group and Condition and an interaction of Group x Condition. We then compared averaged ROI activation within each condition across groups using analysis of variance with follow-up linear contrasts to evaluate the hypothesis of HC > P/AR > FE.

**Hypothesis 2a:**

To analyze to what extent the abnormal engagement of the DLPFC is related to individual cognitive performance in the P/AR and FE groups, we created composite scores using T scores for each of the selected neuropsychological tests (executive functioning, memory, processing speed, attention and working memory). Nine out of ten prodromal individuals and all 12 individuals with First Episode psychosis underwent neuropsychological testing. Composite scores for each domain were then correlated with
mean brain response in the DLPFC region of interest that was found to be task-related across groups.

**Hypothesis 2b:**

To analyze to what extent the magnitude of emotional brain processes is related to individual emotion identification performance we correlated individual accuracy scores (percent correct) on the emotion identification task (completed outside the scanner) with mean amygdalar activation in P/AR and FE groups.

**Hypothesis 2c:**

We investigated the relationship between mean amygdalar activation in P/AR and FE groups and measures of both emotional distress and sleep quality. Emotional distress was characterized as the sum of depressive and anxiety scores as measuring by the Beck Depression Inventory-2 and Beck Anxiety Inventory and sleep quality was assessed with the PSQI.

**Hypothesis 2d:**

We correlated mean brain response in working memory-related regions of the DLPFC to the Global Assessment of Functioning (GAF) score in order to analyze to what extent engagement of the DLPFC is related to individual global functioning in prodromal and FE groups. Similarly, we correlated individual GAF scores with mean amygdalar
activation to analyze to what extent response of the amygdala during the emotional matching task is related to individual global functioning.

Exploratory Analyses:

We also examined how the region of interest results were integrated across the two tasks. Based on the results of this analysis, we used the median of the mean magnitude of brain activation across both tasks to divide P/AR and FE participants into ‘high and low activators’ and then explored group differences in relation to clinical variables.

Finally, we conducted whole brain, voxel-based analyses of both tasks to examine potential differences between P/AR and FE separately compared to HC in regions outside the a priori hypothesized ones. For the VWM task, we focused on differences between the groups in the brain’s linear response to increasing load (9>7>5>3) and for the Emotion Matching task, we focused on the brain’s response during the ‘happy’ and ‘angry’ conditions. For the whole-brain analyses, we considered clusters of group difference to be significant if each voxel in the cluster was significant at the p < 0.05 level (one-tailed) with a cluster volume of 2016 mm$^3$. This cluster-threshold combination protected a whole-brain probability of false positives of p < 0.05.
RESULTS

Clinical Characteristics:

As shown in Table 1, first episode patients reported experiencing more frank psychotic symptoms such as hallucinations when compared to the prodromal group as measured by the SAPS ($t(21) = -2.07, p = .05$). Also, patients with first episode psychosis indicated a significantly higher level of overall negative symptoms as measured by the SANS ($t(21) = -1.98, p = .05$). Specifically, the first episode group endorsed more symptoms of affective blunting ($t(21) = -2.37, p < .05$) and avolition ($t(21) = -3.25, p < .05$). There were no statistically significant differences between the prodromal and first episode patients in regards to the clinician rated index of psychotic symptoms on the BPRS and levels of self-reported depression and anxiety were similar.

The healthy comparison group reported fewer symptoms of depression and anxiety than the prodromal and first episode patients. Healthy individuals endorsed lower levels of both depression ($t(18) = 3.7, p < .05$) and anxiety ($t(18) = 3.0, p < .05$) symptoms when compared to prodromal individuals. Symptoms of depression were also significantly less endorsed in the healthy group compared to the first episode patients ($t(19) = 2.5, p < .05$).
Pre-Scanning Measures of Cognition and Emotion Processing:

Neuropsychological Performance:

Table 2 presents summary statistics for performance on the neuropsychological tests among the P/AR and FE groups. The neuropsychological profile of our FE group was consistent with cognitive profiles of first episode patients reported in the general literature (Lappin et al., 2007; Galderisi et al., 2009). Within the prodromal group, means across all cognitive domains are similar to results of ultra high risk individuals reported by Niendam and colleagues (2006). However, our prodromal group illustrated better cognitive performance than reported by Eastvold and colleagues. (2007). Both FE and P/AR groups had higher overall premorbid IQ levels than in the Eastvold study. Group comparison analyses suggested that FE patients performed significantly worse than P/AR individuals on a task measuring attention as well a test of speed of information processing. There were no significant differences between the P/AR and FE groups in memory, executive functioning and Premorbid IQ levels (Table 2).

Performance on the Facial Emotion Identification Task:

There were significant group differences in reaction time when participants were asked to identify the emotion of a face during the facial emotion identification task \( F(2,132) = 15.2, p<.001 \) (Figure 5; Table 3). Across all four conditions, FE patients had longer reaction times, i.e. took longer to identify the correct facial emotion, when compared to P/AR participants \( t(90)= -3.2, p<.01 \) and healthy individuals \( t(90)= 4.0, \)
Analyses did not reveal any significant differences between the P/AR and HC group (Table 3). The FE slowing was not unique to the emotion conditions, but was also present in the shape identification condition to a similar degree; there was no Condition x Group interaction ($F(6, 132)= .26, p=.96$). Accuracy of identifying sad emotions was lower among the FE group than the HC group ($t(90)=-2.7, p<0.01$), but across all other conditions all participants were equally accurate at identifying emotions (Table 4), suggesting that FE patients may have made a trade-off between accuracy and reaction time for these conditions, slowing down in order to perform more accurately.

Behavioral Performance during the Imaging Tasks:

**Verbal Working Memory Challenge:**

We compared the three study groups on both reaction time and accuracy on the VWM task completed in the scanner. Table 5 shows mean reaction time for all four loads of the working memory challenge. There was a main effect of Group ($F(2,132) = 5.3, p<.01$), with FE participants showing slower reaction times than the P/AR and healthy groups. We also found a main effect of Load ($F(3,131) = 6.1, p<.001$) with differential reaction time across loads 3, 7 and 9. We did not find any Group x Load interactions ($F(6,132)=.68, p=.67$). Accuracy scores are presented in Table 6 for all loads during the working memory task. In general, the FE group was slightly less accurate for
all of the loads, as reflected in the significant main effect of Group \((F(2,132)=6.8, p<.01)\), and there was no Group x Load interaction \((F(6,132)=.69, p=.65)\).

Behavioral Performance during the Facial Emotion Matching Challenge:

Table 7 shows accuracy and reaction times for all conditions of the emotion challenge across all three groups. Data of participants with two runs of the emotional challenge were averaged. Once again the F/E group was slightly slower and less accurate for all conditions, but analyses revealed no main effect of Group and Group x Condition interactions for reaction time and accuracy also were not significant \((F(6,124)=.54, p=.78; F(6,124)=.13, p=.99)\).

Brain Response Analyses

Hypothesis 1a -- Working Memory Challenge Group Differences:

Within the left MFG region where all groups had task specific activation (Figure 3), the magnitude of brain activation was different across loads, that is there was a main effect of Load \((F(3,132)= 2.6, p<.05)\) with magnitude of brain activation generally increasing linearly across loads (Figure 6). We did not however find a main effect for
Group ($F(2,132)=1.6, p=.21$) and there was also no Group x Load interaction ($F(6,132)=0.20, p=.99$).

Hypothesis 1b -- **Emotional Face Matching Group Differences:**

The comparison of brain activation in the amygdala during the emotional face matching challenge for each emotion condition revealed a significant effect of Group for both hemispheres (left: $F(2,102)=5.17, p<.01$; right: $F(2,102)=5.6, p<.01$). Follow-up contrasts revealed that, regardless of emotion condition, there were statistically significant differences in activation between FE individuals when compared to P/AR individuals (left: $t(64)=-2.7; p<.01$, right: $t(64)=-2.6, p<.05$) and healthy individuals (left: $t(70)=2.8; p<.01$, right: $t(70)=2.9, p<.01$). In contrast to our hypothesis, the FE group showed greater activation in both hemispheres, followed by the P/AR group and healthy individuals. There were no significant differences in magnitude of activation between healthy individuals and P/AR individuals in the left or right hemisphere (Figure 7). There was no main effect of Condition ($F(2,102)=.06, p=.95$) and we did not find a Group x Condition interaction in either hemisphere (left: $F(4,102)=1.1, p=.34$; right: $F(4,102)=1.8, p=.13$).
Hypothesis 2a -- Relationship between Brain Activation during Verbal Working Memory Task and Cognitive Performance:

Initially, we did not find any associations between brain activation and neuropsychological test performance when we looked at associations within the region of task-related activation in the combined FE and P/AR group. However, after examining the scatter plots, we decided to look at each group separately and found that cognitive performance in the attention and working memory domain was related to brain activation in both groups, but in a different direction. In the P/AR group higher attention and working memory scores were related to less activation, \( r(8) = -0.86, p<0.01 \); whereas, in the FE group, cognitive performance in the attention and working memory was positively related to brain activation \( r(10) = 0.63, p=0.05 \).

Hypothesis 2b – Correlation of Brain Activation during Emotional Matching Task with Measures of Emotion Processing Ability

Contrary to our hypothesis the magnitude of brain response during the emotional face matching (Hariri) task was not related to the participants’ performance on the emotional identification task. There was a trend-level positive relationship between magnitude of emotional brain response in the left amygdala ROI during the ‘fear’ condition and performance accuracy on the EMT ‘fear’ condition \( r (22)=0.41, p=.06 \).
Magnitude of amygdalar brain response during the emotional face matching task was not associated with performance measures (i.e. accuracy or reaction time) of the participants during scanning.

Hypothesis 2c -- Correlation of Brain Activation during Emotional Matching Task with Measures of Emotional Distress and Sleep Quality

One goal of this study was to examine whether we could find any dissociations between patients who have more affective symptoms and patients whose symptoms are more typical of non-affective psychosis. Significant dissociations may suggest that the heterogeneity in the group relates to different diagnostic prognosis, i.e. patients with more affective symptoms may go on to develop bipolar disorder or psychotic major depression whereas prodromal and first episode patients with less affective symptoms will be more likely diagnosed with typical schizophrenia. In our sample, we found that patients who had a tentative or actual diagnosis of schizophrenia-like psychosis indicated lower levels of emotional distress compared to patients with a tentative or actual diagnosis of psychosis with affective features ($r(21)=.58, p <.01$). Thus, we used emotional distress as a potential indicator or proxy for affective disturbance and examined its relationship to brain activation in the right and left amygdala during the emotional face matching task conditions. We found a significant association between left amygdala brain activation and emotional distress. Individuals with high emotional distress also had higher brain activation in the left amygdala during the angry condition.
(r(21)=0.46, p < .05; Figure 8). There were no other significant association between amygdala activation and emotional distress (Table 8).

Another potential proxy for risk of future affective versus non-affective psychosis may be sleep disturbance, since sleep problems are one of the main symptoms of bipolar disorder, specifically, the decreased need to sleep. Consistent with this, in our sample, participants with more current affective features indicated significantly more sleep disturbance, (t (15)=-2.2, p<.05). In addition, there were group differences, though only at trend level, in two out of seven components of the PSQI. Overall, there was a trend for lower sleep duration (t(15)=-1.9, p=.08) and efficiency (t(15)=-1.7, p=0.1) in patients with possible affective psychosis. Significant associations were also found between level of emotional distress and sleep quality. All but two components of the sleep quality indices were associated significantly with emotional distress level (Table 9).

We thus examined whether any of the sleep quality components that were found to differentiate between the groups were associated with functional brain activation in the
amygdala. Patients with low sleep efficiency had significantly higher brain activation in the right amygdala during the ‘happy’ condition ($r(17) = -.63, p < .01$) and bilaterally in the ‘angry’ condition (right amygdala: $r(17) = -.47, p = .05$, left amygdala: $r(17) = -.49, p < .05$).

**Hypothesis 2d -- Correlation of Brain Activation During the Verbal Working Memory Task and Emotion Matching Task with Global Functioning**

Within the combined P/AR and FE group, magnitude of brain response during the verbal working memory challenge task was related to global functioning. Specifically, there was a positive association between global functioning as measured by GAF and brain response in the left MFG for loads 3 and 5 ($r (22) = .51$ and $r (22) = .46, p < .05$) and trend-like associations for load 9 and when all loads were averaged ($r (22) = .38, p = .09$ and $r (22) = .42, p = .06$) (Figures 9).

**Insert Figures 9 Here**

Magnitude of brain response of the amygdala during the emotional matching task was also related to individual global functioning. Correlational analyses revealed a significant negative relationship between GAF and the magnitude of activation in the left amygdala during the ‘angry’ condition ($r (22) = -.43, p < .05$) (Figure 10).

**Insert Figure 10 Here**

**Relationship Between Activation on Two Tasks:**
Additionally, we explored the relationship between magnitude of brain activation during the cognitive challenge and the emotional face matching challenge within the combined P/AR and FE groups. Individuals with greater right amygdala activation during the ‘happy’ condition of the emotional face matching challenge showed more left MFG response to all loads compared to baseline in the VWM task (load 3: \( r(21) = 0.41, p = 0.05 \); load 7 \( r(21) = 0.62, p < 0.01 \); load 9 \( r(21) = 0.53, p < 0.05 \)) although the relationship was only trend like in load 5 \( r(21) = 0.36, p = 0.10 \)(Load 7 presented in Figure 12). This suggested that there were generally “good activators” and “poor activators” within the clinical groups.

To follow up on this unexpected finding, we explored whether there were differences between good and poor activators on other variables (mood ratings and clinical ratings). Individuals who were high activators, i.e. showed greater activation on both imaging tasks, tended to generally have fewer positive symptoms and lower overall clinician rated psychiatric symptoms (BPRS) although, in this preliminary sample, none of the relationships reached statistical significance and were only trend like (Table 10).

**Exploratory Whole-Brain Analysis:**

Exploratory analyses revealed several significant clusters of activation when comparing healthy individuals to first episode patients or prodromal individuals during
the linear contrast (3>5>7>9) of the working memory challenge \((p=0.05\), cluster volume 2016mm\(^3\); (Table 11). Specifically, prodromal individuals compared to healthy individuals showed reduced activation in the bilateral superior temporal gyrus and medial frontal gyrus, left cingulate gyrus, bilateral inferior frontal gyrus, bilateral postcentral gyrus, and right precuneus (Figure 12).

FE individuals also showed reduced brain response compared to healthy individuals in several brain regions (Figure 13). We found significantly different brain activation in the left supramarginal gyrus, right middle frontal gyrus and right superior frontal gyrus.

There were also clusters of differential activation between groups during the happy and angry conditions of the emotional face matching task. Overall, the first episode patients showed significantly increased activation in the right lingual gyrus and cuneus, left cingulate gyrus and parahippocampal gyrus as well as bilateral precuneus and superior temporal gyrus during the ‘happy’ condition. Also, the FE group had more activation than healthy controls in the right cuneus during the ‘angry’ condition.
When we compared brain activation of the prodromal individuals to healthy controls we found that the P/AR group showed deactivation in the right superior parietal lobule, increased activation in the left fusiform gyrus and right middle frontal gyrus during the ‘angry’ condition. There were no significant clusters between these groups during the ‘happy’ condition.

Insert Table 12 Here

Insert Figure 14 & 15 Here
DISCUSSION

In order to begin to understand how cognitive and emotional symptoms of schizophrenia arise, we compared brain functioning associated with emotional as well as cognitive processes in groups of individuals who exhibited early and sub-threshold symptoms of psychosis to patients in their early phases of psychosis and/or immediately after their first psychotic episode and to healthy individuals.

Neural Systems Implicated in Basic Cognitive and Emotional Processes in the Prodrome and Early Psychosis

As expected, all individuals showed increasing activation in the DLPFC, specifically left MFG, during the verbal working memory challenge as the load increased. Contrary to our expectations, however, load-related brain activation across all three groups was similar, i.e., magnitude of brain activation in the left MFG during the VWM challenge in both prodromal and first episode patients was comparable to that of healthy individuals. The present findings are inconsistent with previous studies that document hypoactivation in the DLPFC and specifically the MFG in individuals with high risk for psychosis (Whalley et al., 2005.; Keshavan et al., 2002) as well as in first episode psychosis patients (Tan et al., 2005; Mendrek et al. 2004; Riehemann et al., 2001) during working memory tasks.

While we did not find altered activation in our ‘region of interest,’ we did find differential load-related activation when examining activation patterns using whole brain
analyses. Therefore, our results confirmed previous findings of differential activation in
the P/AR as well as FE groups when compared to healthy individuals. Consistent with
previous studies (Morey et al. 2005; Keshavan et al., 2002; Pantelis et al., 2007), we
found hypoactivation in several brain regions when we compared prodromal individuals
to healthy controls. While some areas of differential activation were within frontal brain
regions (e.g., bilateral inferior frontal gyrus), the P/AR group showed less activation in
temporal cortical and subcortical brain regions as well. Similarly, as suggested in
previous studies, the FE group demonstrated predominantly hypoactivation rather than
increased activation relative to healthy individuals (Fusar-Poli et al. 2007) in several
regions.

Several of these regions, for example the cingulate gyrus although part of the
limbic system are involved in executive control. Specifically, studies suggest that the
anterior cingulate gyrus is part of a neural system involved in attention (Cameron et al.,
1997), a function necessary and likely intertwined in the present working memory
paradigm. Moreover, structural MRI studies in patients at risk for psychosis have
revealed smaller anterior and posterior cingulate volumes when compared to healthy
individuals (Pantelis et al., 2003b; Borgwardt et al., 2007a&b). Additionally, reduced
gray matter in the anterior and posterior cingulate was predictive of later conversion to
psychosis. Thus, findings of aberrant brain activation in these regions are not surprising
but rather underscore the idea that multiple brain regions are part of an interacting
system.
Our findings using whole-brain analyses also suggest that we may have been more conservative than other studies when choosing our initial region of interest. The prodromal group as compared to healthy controls for example demonstrated less activation in the inferior frontal gyri (IFG), areas that while part of the DLPFC are not included in it in their entirety. Yet, studies have shown the involvement of IFG in working memory associated tasks (Fusar-Poli et al., 2007).

We found differences in amygdalar brain activation during the emotional challenge but, in contrast to our hypothesis, there were no differences between healthy and prodromal individuals, and we found increased magnitude of amygdalar activation in the FE group. While abnormal brain activation during emotional processes in psychosis has been documented before, most studies found amygdalar hypoactivation in patients in response to emotional stimuli (Gur et al., 2002a; Hempel et al., 2003; Holt et al., 2006a; Schneider et al., 1998; Taylor et al., 2002). Some studies have however found hyperactivation in temporal brain regions including the hippocampus and amygdala (Hempel et al., 2003; Holt et al., 2006a; Kosaka et al., 2002; Russell et al., 2007) and our results are consistent with these previous studies. Furthermore, in keeping with former studies (Gur et al., 2002a; Kosaka et al., 2002, Seifert et al. 2008), we found no behavioral performance differences across the groups. Our findings suggest that despite similar behavioral performance across all groups, FE patients showed hyperactivation in the amygdala especially in the ‘happy’ and ‘angry’ conditions. The absence of behavioral performance differences suggests that the right and left amygdala of patients who have already converted to psychosis need to work ‘harder’ to achieve the same behavioral
performance (i.e. identify emotional faces) as healthy individuals and patients who are in the prodrome but have not yet converted. While a theory of compensatory mechanisms is best illustrated with tasks of varying levels of difficulty and their associations to brain activation, we nevertheless found significant positive association between behavioral performance and activation that suggest that the FE group’s hyperactivation is likely compensatory in nature, especially considering that behavioral performance was similar across all groups. This idea is further strengthened by our finding that FE individuals displaying higher amygdalar activation also were more accurate during the emotion identification task. Moreover there was also a positive relationship in behavioral performance between the two emotional tasks of emotion identification and matching.

The lack of significant differential brain activation in the amygdala between the P/AR and HC group in the present study is interesting and contrary to our assumption. It is, however, consistent with a recent study that was also unable to find differences in brain functioning in the amygdala but reported hyperactivation in high-risk individuals in the right lingual and fusiform gyrus, the left middle occipital gyrus, the inferior and superior frontal gyri, the cuneus, the thalamus and the hippocampus during a similar emotion discrimination task (Seifert et al., 2008). In accord with Seifert and colleagues, we also found increased activation in the prodromal group compared to healthy individuals in the left fusiform gyrus and frontal gyri using whole brain analyses. These results mimic findings in structural neuroimaging studies that report more substantial volumetric and biochemical changes in cortical rather than subcortical brain regions in populations at high risk for psychosis (Velakoulis et al., 2006, Pantelis et al., 2009).
Decreased grey matter volumes in inferior frontal, temporal and mid-cingulate in at-risk individuals for example has been shown to be predictive of conversion (Pantelis et al., 2003). Similarly, an accelerated rate of grey matter retraction in prefrontal cortical areas has been recently documented in pre-psychotic ultra high-risk individuals and at the very earliest stages of psychosis (Sun et al., 2008, 2009). Thus, evidence of compromised subcortical integrity, in this case in the amygdala, may not be a premorbid illness marker but rather may be related to the progression of the illness. In such, while structural, functional and neurochemical abnormalities in frontal brain regions for example are trait-like and hence present in at-risk individuals other abnormalities and changes may be state-dependent and progress with the illness or at the time of the illness.

In addition to understanding differences in functional brain profiles between groups that fall at different places along the psychosis spectrum and in healthy individuals, we sought a richer understanding of how individual differences in clinical and cognitive variables would relate to brain functioning. Thus, we also examined associations of brain profiles with relevant behavioral variables.

Associations between Differential Brain Activation, Cognitive and Clinical Correlates and Global Functioning

We did not find any associations between brain activation and cognitive performance in the combined FE and P/AR group, but when we looked at each group separately, cognitive performance on the attention and working memory domain, as hypothesized, was related to brain activation in both groups. These findings underscore
previous findings that show associations between cognitive impairments and underlying brain anomalies in psychosis (Honey et al. 2005; Jafri et al. 2008; Kim et al. 2009; Liang et al. 2006; Liu et al. 2008; Schlosser et al. 2003). This association is especially intriguing in face of the group difference in the attention domain and suggests that even in the prodromal group (which illustrated intact attention and working memory on average), those individuals who have poor attention and working memory show less activation during the VWM challenge. Interestingly, the direction of the relationship between attention/working memory was different for each group. Prodromal individuals who performed better on tasks of attention and working memory had less LMFG brain activation but high performing FE patients had higher brain activation. This discrepancy may suggest that while in the P/AR group activation is related to efficiency, this relationship is reversed in the FE group indicating compensation. Surprisingly, previous studies in at-risk populations (e.g., Callicott et al., 2003; Seidman et al., 2006) have not examined the association between neuropsychological performance and brain activation thus it is difficult to determine whether these findings are clinically significant. These more efficient P/AR individuals for example may never convert and this efficiency is possibly inversely related to conversion. A longitudinal follow-up on these individuals would be interesting and could elucidate whether this ‘efficiency’ is state-dependent and will disappear during conversion to psychosis or whether in fact it is associated with low possibility of conversion.

As expected, we found several associations between global functioning and magnitude of brain response during the emotional as well as cognitive challenge. In the
combined group (P/AR and FE), individuals with higher levels of LMFG activation during the VWM challenge were globally higher functioning. In the amygdala, however, greater activation was associated with lower levels of global functioning. Again, we found group differences, as DLPFC activation was only significantly related to global functioning in prodromal individuals whereas amygdala activation was related to global functioning only in the FE group.

While behavioral performance on measures of cognition and emotion have been linked to global functioning before (for a review see: Niendam, Jalbrzikowski & Bearden, 2009), our findings extend these associations and highlight that more basic neurobiological abnormalities likely account for overall global functioning. Although our study design does not permit conclusions about the specific mechanisms underlying these systems, our findings provide evidence that the interplay of the emotional and cognitive systems is dysregulated along the psychosis spectrum. The degree and nature of dysregulation appears to be related to the stage or course of psychosis. One might speculate that the integrity of both systems independently may not be integral for global functioning at the early stages of psychosis, i.e. during the prodrome as long as the system’s interplay can be regulated. Thus, while both systems may be compromised, the ‘dialogue’ between the systems is still intact and regulation of the greater system can take place (Figure 16). For example, up-regulation of frontal systems including the MFG in prodromals compensates for or ‘normalizes’ their amygdala deficits. Consequently, these individuals are still able to globally function adequately. Break down in regulation takes place once both the integrity of each system as well as the interplay of the systems with
each other is compromised, which in turn leads to psychosis and poor global functioning. Degree of dysregulation can possibly explain why some prodromal individuals continue to develop psychosis while others do not. This lends evidence to the idea that the prodrome invariably leads to progression and the notion that early prodromal symptoms necessarily mean that an illness is already established (Yung et al. 1996; Mojtabai et al., 2003).

As previously mentioned in the introduction, there is little research studying the integrity or interplay of both emotional and cognitive systems together even in chronic schizophrenia. Recent research by Pauly and colleagues (2009) investigated the interaction of working memory and emotion in individuals at high risk for psychosis and concluded that cerebral dysfunction related to cognitive and emotional processes, as well as their interaction, can emerge in individuals at risk for psychosis. While Pauly et al. examined emotion and cognition within the same group, their study used mood induction using different smells to look at cognitive brain correlates related to emotion. The necessity to examine global functioning in light of both emotional and cognitive mechanisms and their interaction in psychosis becomes more apparent when considering that neurocognition alone only accounts for 20% to 40% of global functioning (Couture et al. 2006) and that social cognition plays an integral part in global functioning (Sergi et al. 2007). Thus, to understand the neurobiological etiology of psychosis it is vital for future studies to examine emotion and cognition functioning concurrently. Studies
looking at both systems could be augmented by research combining multiple investigation techniques such as examining associations between functional brain correlates to structural brain changes. Also intriguing is the prospect of studying white matter integrity of emotional and cognitive systems in psychosis. Such an approach could potentially elucidate underlying changes in white matter that are responsible for dysregulation of the overall system.

**Possible Implications of Studying Heterogeneity in Psychosis**

In the introduction we noted that there is a large amount of heterogeneity along the psychosis spectrum. Early in the course of psychosis, some patients present with varying degrees of affective as well as cognitive symptoms, while others only display cognitive symptoms. Furthermore, some patients suffer from sleep disturbance in addition to mood and cognitive symptoms. This heterogeneity in the early stages can be predictive of the future course of the disorder and it is at times the basis for differential diagnosis.

One goal of research along the psychosis spectrum is to help inform diagnostic considerations, such as by identifying the nature of psychosis (i.e, non-affective vs. affective). While this study did not set out to specifically examine the relationship between brain activation, diagnosis and clinical variables, our data lent itself well to exploring this relationship. Thus, we looked at associations between brain activation, behavioral performance during emotional tasks and affective proxies. Patients who had more emotional distress showed greater left amygdala activation. More affective distress
was also predictive of poorer performance on the Emotion Identification Task.
Furthermore, those with higher affective distress also reported more sleep disturbance.
Interestingly, those patients with high affective distress had a preliminary diagnosis of bipolar disorder and patients with lower affective distress had a tentative clinical diagnosis of schizophrenia. Our findings are not surprising when considering that disruptions in affect and sleep are reported to be the most commonly observed symptoms in the early phases of bipolar disorder (Lish et al. 1994; Hirschfeld, Lewis & Vorink, 2003; Conus et al., 2008). However despite numerous reports describing the clinical picture and initial symptomology of psychosis, underlying brain correlates are rarely investigated. Even more scarce are studies examining the long term course of early psychosis and the subsequent differentiation and transition to schizophrenia or bipolar disorder. This is despite increasing knowledge that advances on the phenomenology of premorbid features and the subsequent development of either schizophrenia or bipolar disorder provide opportunities to reduce the incidence, postpone the onset, and/or improve the long-term course of the disorders.

Early intervention programs in psychosis have been receiving increasing attention within the past decade (Comblatt and Malhotra 2001; Heinssen et al. 2001). These early interventions are not limited to pharmacological treatments but a number of studies have also looked at the effectiveness of behavioral interventions during the prodrome (Lam, Wong & Sham, 2001). However, pharmacological and behavioral interventions will be most effective if aimed at the processes that cause psychosis. This demands increasing the knowledge base about the biological processes, or at least their correlates, that cause
psychosis related disorders. The present findings are thus encouraging as they highlight the significance of studies that investigate multiple dimensions of psychosis concurrently. These data also shed some light for future studies in this area and speak to early predictive diagnostic potential of brain correlates in association with clinical variables.

Limitations:

There are several limitations to this study that should be noted. Although our sample size is similar to other imaging studies, it nevertheless is a potential weakness of the present study. The small sample size is of specific concern when we consider the high number of variables (e.g., clinical, behavioral, demographics) we sought to explore. Multiple comparisons often lead to false positives, and therefore Type I errors can not be excluded. It is comforting, however, that many of our findings are supported by existing literature, decreasing the likelihood that these are false positives. Nevertheless, future studies are necessary to replicate these findings.

On the other hand, the relatively small sample size may have also limited our statistical power to find group differences. Some relationships (e.g. BPRS and brain activation) for instance failed to reach statistical significance but were trend-like. On the other hand, we found several relatively robust associations in spite of our small sample size (e.g. relationship of brain activation between both imaging tasks) that are probably more meaningful in light of this limitation and are less likely to represent statistically significant, but not clinically relevant, findings.

Furthermore, neuroimaging studies pose an additional challenge regarding power and sample size predominantly due to the considerable multiple comparisons among tens
of thousands of correlated voxels that can lead to Type 1 errors. To ameliorate this issue, we used Monte-Carlo simulations to identify cluster size. Moreover, we constricted our main analyses to specific regions to reduce the severity of correction for multiple tests and instead correct only for a small number of ROIs, for instance the amygdala.

It should be noted, however, that while using ROIs for statistical control is widely implemented in neuroimaging research, the question of how to measure signal within the ROI is still of debate (Poldrack, 2007) specifically in larger more heterogeneous brain regions, risking contamination of signal with noise as well as cancelation of activation and deactivation. In the present study, however, we believe that selecting the amygdala as our region of interest is justified for several reasons. For one, the amygdala is a relatively small brain region that is found time and again to be functionally associated with emotion. Furthermore, we did not average or blur our signal across this region thus minimizing the aforementioned risks.

The second major limitation of the present study is its cross-sectional study design. Using a cross-sectional design is common in research and in many instances a cross-sectional design is desirable as it circumvents disadvantages associated with longitudinal designs including cost, attrition and time. In addition, cross-sectional studies are well suited for examining outcomes of mental illness for example. The cross-sectional nature of the present study, however, does not allow for causal inferences. While our results nicely describe brain activation patterns, cognitive and emotional functioning as well as the social functioning in patients and healthy controls and further characterize differences between the groups, we can only speculate about the mechanism of change
and the temporal and developmental trajectory of the psychosis prodrome to the onset of psychosis. To fully understand the progression of schizophrenia or psychosis, it is necessary to study change within the same group of individual and compare their brain function at each stage of the disorder. Nevertheless, the present study is the first to examine emotional, cognitive and social functioning concurrently in the prodrome as well as during the first episode of psychosis. Thus, we hope that our findings have added to the knowledge base in psychosis research. At the same time, the nature of the larger study allows longitudinal follow-up of some of our participants hence creating the possibility for future longitudinal investigations.

Finally, in the present study, we were unable to replicate some prior research findings (e.g., differences in HC and P/AR in brain activation in the MFG). Whether this is a valid limitation of this study is debatable considering that this area of research is still in its infancy and that the existing findings are still inconclusive and scarce. One major confound and challenge of previous studies as well as of the present study may be appropriate task selection, that is paradigms that have construct validity and concurrently elicit sufficient signal strength for imaging studies.

Strengths:

Nevertheless there are several strengths to the present study. First and foremost, this is the first study to our knowledge to study emotional and cognitive functioning in the psychosis prodrome. Furthermore, our study design allowed us to compare our findings in the prodrome to first episode patients and healthy controls and thus gave us
the opportunity to explore emotional and cognitive neural correlates specific to the prodrome as well as early psychosis. All three groups were also well matched demographically, further facilitating the comparison across groups and suggesting that the presence of differences across groups is not likely due to differences in age or years of education for example. Our participants also performed similarly on all but one of the behavioral measures. For example, reaction time and accuracy were similar across groups for the emotional face matching task and emotion identification task. The absence of behavioral performance differences suggests that the chosen tasks represented an ‘even playing field’ for all participants highlighting that the presence of brain activation differences at least for emotion processing are not confounded by performance differences but are rather specific to anatomical or functional brain changes.

Yet another strength of the present study is the use of multiple tasks to measure and capture the same construct. We set out to measure emotional and cognitive functioning inside the scanner but we also correlated our data with tasks that the participants completed outside of the scanner. We found positive correlations between the performances across these tasks confirming construct validity for our emotional and cognitive tasks and further strengthening our aim to measure brain changes associated with emotion and cognition.

Finally, this study explored associations between brain functioning and other variables of interest thought to be affected during psychosis as well as the prodrome. This was done to look at the cognitive and affective heterogeneity of the population. As such we were able to investigate associations between neural correlates and global functioning
for example. We were also able to explore the relationship of sleep and mood with brain functioning for instance as a first attempt to approximate an affective or bipolar-like psychosis. While it is too early to draw firm conclusions about our findings, the present study provides some insight into possible future studies in the field.

Conclusions

Our unique study design allowed us a small glimpse at neural systems underlying working memory and emotion regulation at different stages of the psychosis prodrome compared to healthy individuals. Both clinical groups exhibited abnormal amygdala activation when compared to healthy individuals but differential brain activation during the working memory challenge was only observed in the FE group. The present results suggest that both systems are implicated in psychosis. Further analyses suggested that brain response was associated with neuropsychological performance as well as overall global functioning scores. Our results could be interpreted as supporting a dysregulation hypothesis of psychosis. Global functioning is compromised as a function of disruption in the regulatory mechanisms between cognitive and emotional systems.
APPENDIX

Figure 1: Verbal Working Memory Task
Experimental condition:

Sensorimotor control condition:

Figure 2: Facial Emotion Matching Task
Figure 3: Area of significant Brain Activation during the Verbal Working Memory Challenge in the Left Middle Frontal Gyrus Common to Experimental and Comparison Groups
Figure 4: Mean Fit Coefficient in the All-Loads Condition across Groups in the Region of Common Response
NOTE: * = P<.05

Figure 5: Mean Reaction Time during Emotional Morphing Task across all three Groups
Figure 6: Magnitude of Brain Activation Across all Loads during the Verbal Working Memory Challenge in the Region of Common Brain Response
NOTE: ** p<.01, * p<.05, + trend-like

Figure 7: Left and Right Amygdala Brain Activation during Emotional Face Recognition Challenge
Figure 8: Relationship between Left Amygdalar Brain Activation ('angry') and Emotional Distress
Figure 9: Association between GAF scores and brain response in the left MFG during load 3 in the P/AR and FE (combined)
Figure 10: Association between GAF scores and the magnitude of activation in the left amygdala during the ‘angry’ condition in P/AR and FE (combined)
Figure 11: Association between Brain Activation in the R Amygdala during the ‘happy’ condition and Brain Activation in the L MFG during the ‘load 7’ condition Verbal Working Memory Challenge (3-5-7-9 Linear Load)
Note: HC > P/AR, $p<.05$

Figure 12: Regions of Differential Brain Activation between HC and P/AR during the Verbal Working Memory Challenge (3-5-7-9 Linear Load)
NOTE: HC > FE, p<.05

Figure 13: Regions of Differential Brain Activation between HC and FE during the Verbal Working Memory Challenge (3-5-7-9 Linear Load)
Note: FE > HC, \( p < .05 \)

Figure 14: Regions of Differential Brain Activation between HC and FE during the Emotional Face Matching Challenge (‘Angry’ Load)
Note: Red: HC > P/AR, $p<.05$
      Blue: P/AR > HC, $p<.05$

Figure 15: Regions of Differential Brain Activation between HC and P/AR during the Emotional Face Matching Challenge (‘Angry’ Load)
Functional Dialogue/ Regulation between Intact Cognitive (Dorsal) and Emotional (Ventral) Systems in Healthy Individuals

![Diagram of Dorsal and Ventral Systems]

Functional Dialogue/ Up/Down-Regulation between Defective Systems in Prodromal Individuals

![Diagram of Dorsal and Ventral Systems with arrows indicating regulation]

Dysregulation/ Absence of Dialogue between Defective Systems in First Episode Patients

![Diagram of Dorsal and Ventral Systems with arrows indicating dysregulation]

Note: Dark dashes indicate Defective System

Figure 16: Hypothetical Regulation of Cognitive and Emotional Systems
Table 1: Demographic and Clinical Variables among Prodromal Patients, First Episode Patients and Healthy Comparison Groups

<table>
<thead>
<tr>
<th></th>
<th>Healthy Individuals</th>
<th>Prodromal Patients</th>
<th>First Episode Patients</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Summary Statistic</td>
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<tr>
<td></td>
<td></td>
<td>(Mean(SD) or Ratio)</td>
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</tr>
<tr>
<td><strong>Demographic Variables</strong></td>
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</tr>
<tr>
<td>Age (years)</td>
<td>12</td>
<td>23.0 (4.6)</td>
<td>10</td>
</tr>
<tr>
<td>Sex (M:W)</td>
<td>12</td>
<td>6:6</td>
<td>10</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12</td>
<td>16.4 (4.4)</td>
<td>10</td>
</tr>
<tr>
<td>Handedness (R:L)</td>
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<td>10:2</td>
<td>10</td>
</tr>
<tr>
<td>Marital Status</td>
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<td>12:0</td>
<td>10</td>
</tr>
<tr>
<td>(single : married)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Variables</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory T-Scores</td>
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<td>41.8 (5.9)*</td>
<td>10</td>
</tr>
<tr>
<td>Beck Anxiety Inventory T-Scores</td>
<td>10</td>
<td>41.4 (4.1)*</td>
<td>10</td>
</tr>
<tr>
<td>Global SAPS</td>
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<td>--</td>
<td>10</td>
</tr>
<tr>
<td>Positive Symptoms</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Global SANS</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>Negative Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS Hallucinations</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>SAPS Delusions</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>SAPS Bizarre Behavior</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>SAPS Formal Thought Disorder</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>SANS Affective Blunting</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>SANS Alogia</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>SANS Avolition</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>SANS Anhedonia</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>SANS Attention</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>BPRS Total</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>GAF</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
</tbody>
</table>
Table Continued

NOTE: $^\circ = H C \neq P / AR, (p < .05)$; $^\dagger = H C \neq F E, (p < .05)$; $^* = H C < P, (p < .05)$; $^\# = H C < F E, (p < .05)$; $^\star = P / AR < F E, (p < .05)$; $^{**} = P / AR < F E, (p < .01)$
Table 2: Cognitive Variables among Prodromal Patients and First Episode Patients

<table>
<thead>
<tr>
<th>Domain</th>
<th>Prodromal Patients (N=9) T-scores (Mean (SD))</th>
<th>First Episode Patients (N=12) T-scores (Mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Functioning</td>
<td>54.0 (6.1)</td>
<td>54.0 (6.7)</td>
</tr>
<tr>
<td>WCST-Errors</td>
<td>40.7 (9.1)</td>
<td>45.3 (9.5)</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>53.7 (7.3)</td>
<td>49.9 (6.7)</td>
</tr>
<tr>
<td>Stroop C-W</td>
<td>53.3 (11.2)</td>
<td>44.5 (12.4)</td>
</tr>
<tr>
<td>Trails B Time</td>
<td>34.7 (23.4)</td>
<td>28.4 (24.5)</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall</td>
<td>42.1 (16.7)</td>
<td>30.8 (11.3)</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognition</td>
<td>46.9 (11.9)</td>
<td>40.2 (15.2)</td>
</tr>
<tr>
<td>Brief Visual Memory Test –Recall</td>
<td>52.4 (10.2)</td>
<td>45.9 (14.9)</td>
</tr>
<tr>
<td>Brief Visual Memory Test –Delayed Recall</td>
<td>52.0 (8.6)</td>
<td>47.7 (14.3)</td>
</tr>
<tr>
<td>Attention</td>
<td>54.4 (5.5)</td>
<td>47.3 (5.3)</td>
</tr>
<tr>
<td>Spatial Span</td>
<td>49.7 (8.6)</td>
<td>48.1 (6.2)</td>
</tr>
<tr>
<td>Letter-Number Sequencing</td>
<td>58.8 (9.7)</td>
<td>46.1 (9.6) *</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>51.1 (7.0)</td>
<td>43.3 (10.0)</td>
</tr>
<tr>
<td>Trails A Time</td>
<td>43.6 (11.3)</td>
<td>37.8 (16.5)</td>
</tr>
<tr>
<td>Digit Vigilance Test Time</td>
<td>55.9 (10.9)</td>
<td>45.9 (14.9)</td>
</tr>
<tr>
<td>Digit Symbol Coding</td>
<td>53.8 (10.7)</td>
<td>43.8 (10.0) *</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>62.2 (14.8)</td>
<td>56.3 (11.9)</td>
</tr>
<tr>
<td>Block Design</td>
<td>59.3 (11.1)</td>
<td>54.8 (12.1)</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>63.8 (14.3)</td>
<td>57.0 (12.0)</td>
</tr>
</tbody>
</table>

* FE<P, p<.05
Table 3: Mean Reaction Time during the Emotion Identification Task (Morphing)

<table>
<thead>
<tr>
<th>Shape</th>
<th>Mean Reaction Time</th>
<th>Standard Deviation</th>
<th>F-statistic</th>
<th>Post-Hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t-statistic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.8**</td>
<td></td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>2567.8</td>
<td>488.3</td>
<td>2.35*</td>
<td>HC &lt; FE</td>
</tr>
<tr>
<td>P/AR</td>
<td>2462.0</td>
<td>474.7</td>
<td>-2.77*</td>
<td>P/AR &lt; FE</td>
</tr>
<tr>
<td>FE</td>
<td>3208.8</td>
<td>809.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happy</td>
<td></td>
<td></td>
<td>3.9*</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>2833.8</td>
<td>350.3</td>
<td>2.83*</td>
<td>HC &lt; FE</td>
</tr>
<tr>
<td>P/AR</td>
<td>2977.0</td>
<td>532.4</td>
<td>Trend</td>
<td>P/AR &lt; FE</td>
</tr>
<tr>
<td>FE</td>
<td>3410.0</td>
<td>614.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sad</td>
<td></td>
<td></td>
<td>4.1*</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>3586.8</td>
<td>459.5</td>
<td>2.83*</td>
<td>HC &lt; FE</td>
</tr>
<tr>
<td>P/AR</td>
<td>3782.2</td>
<td>536.7</td>
<td>Trend</td>
<td>P/AR &lt; FE</td>
</tr>
<tr>
<td>FE</td>
<td>4229.8</td>
<td>631.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fearful</td>
<td></td>
<td></td>
<td>2.9*</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>3532.2</td>
<td>417.4</td>
<td>2.34*</td>
<td>HC &lt; FE</td>
</tr>
<tr>
<td>P/AR</td>
<td>3626.2</td>
<td>539.6</td>
<td>Trend</td>
<td>P/AR &lt; FE</td>
</tr>
<tr>
<td>FE</td>
<td>4047.5</td>
<td>636.0</td>
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</table>

NOTE: HC= Healthy controls (n=10), P/AR= Prodromal/ At risk (n=10), FE = First Episode (n=13), ** = p<0.01, *= p<0.05, + = trend
Table 4: Accuracy during the Emotion Identification Task (Morphing)

<table>
<thead>
<tr>
<th></th>
<th>Mean Accuracy (%)</th>
<th>Standard Deviation (%)</th>
<th>F-statistic</th>
<th>Post-Hoc t-statistic</th>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>70.0</td>
<td>44.0</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>P/AR</td>
<td>79.4</td>
<td>40.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FE</td>
<td>78.8</td>
<td>31.0</td>
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<tr>
<td><strong>Happy</strong></td>
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<td>1.1</td>
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<tr>
<td>HC</td>
<td>98.3</td>
<td>24.0</td>
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<tr>
<td>P/AR</td>
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<td>30.8</td>
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<tr>
<td>FE</td>
<td>91.8</td>
<td>72.0</td>
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<tr>
<td><strong>Sad</strong></td>
<td></td>
<td></td>
<td>3.5*</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>88.8</td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P/AR</td>
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<td>6.9</td>
<td>-2.7**</td>
<td>HC &gt; FE</td>
</tr>
<tr>
<td>FE</td>
<td>82.9</td>
<td>631.1</td>
<td>2.4*</td>
<td>P/AR &gt; FE</td>
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<tr>
<td><strong>Fearful</strong></td>
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<td>.99</td>
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<td>P/AR</td>
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<tr>
<td>FE</td>
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NOTE: HC= Healthy controls (n=10), P/AR= Prodromal/ At risk (n=10), FE = First Episode (n=13), ** = p<0.01, * = p<0.05
Table 5: Mean Reaction Time during the Verbal Working Memory Challenge Task

<table>
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<tr>
<th>Load 3</th>
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<th>Standard Deviation</th>
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<th>Post-Hoc</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.1</td>
<td></td>
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<tr>
<td>HC</td>
<td>1033.7</td>
<td>233.8</td>
<td></td>
<td></td>
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<tr>
<td>P/AR</td>
<td>1104.3</td>
<td>191.0</td>
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<tr>
<td>FE</td>
<td>1223.8</td>
<td>240.3</td>
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<table>
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<th>Standard Deviation</th>
<th>F-statistic</th>
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<tr>
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<td>P/AR</td>
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<td>1303.2</td>
<td>267.1</td>
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<table>
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<th>F-statistic</th>
<th>Post-Hoc</th>
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<tbody>
<tr>
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<td>4.3*</td>
<td></td>
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<tr>
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<td>245.7</td>
<td>2.00*</td>
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</tr>
<tr>
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<td>159.2</td>
<td>-2.77*</td>
<td>P/AR &lt; FE</td>
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<td>FE</td>
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<th>F-statistic</th>
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<td>P/AR</td>
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<td>FE</td>
<td>1418.9</td>
<td>268.2</td>
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</table>

NOTE: HC= Healthy controls (n=12), P/AR= Prodromal/ At risk (n=10), FE = First Episode (n=12), * = p<0.05;
Table 6: Accuracy during the Verbal Working Memory Challenge Task

<table>
<thead>
<tr>
<th>Load 3</th>
<th>Mean Accuracy (%)</th>
<th>Standard Deviation (%)</th>
<th>F-statistic</th>
<th>Post-Hoc t-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Load 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>94.4</td>
<td>7.4</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>P/AR</td>
<td>94.2</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FE</td>
<td>87.1</td>
<td>10.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Load 5</td>
<td></td>
<td></td>
<td>4.0*</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>93.8</td>
<td>9.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P/AR</td>
<td>97.5</td>
<td>4.0</td>
<td>2.35*</td>
<td>P/AR &gt; FE</td>
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<tr>
<td>FE</td>
<td>81.8</td>
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<tr>
<td>Load 7</td>
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<tr>
<td>HC</td>
<td>84.7</td>
<td>18.1</td>
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<td></td>
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<tr>
<td>P/AR</td>
<td>84.2</td>
<td>13.9</td>
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<td></td>
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<tr>
<td>FE</td>
<td>72.0</td>
<td>16.4</td>
<td></td>
<td></td>
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<tr>
<td>Load 9</td>
<td></td>
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<td>.74</td>
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</tr>
<tr>
<td>HC</td>
<td>66.0</td>
<td>14.5</td>
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<td></td>
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<tr>
<td>P/AR</td>
<td>59.2</td>
<td>17.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FE</td>
<td>59.1</td>
<td>14.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: HC= Healthy controls (n=12), P/AR= Prodromal/ At risk (n=10), FE = First Episode (n=12), * = p<0.05;
Table 7: Mean Reaction Time and Accuracy during in the Emotional Face Matching Challenge (Hariri)

<table>
<thead>
<tr>
<th></th>
<th>Reaction Time</th>
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<th>Accuracy</th>
<th></th>
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</thead>
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<tr>
<td></td>
<td>Mean</td>
<td>Standard</td>
<td>Mean</td>
<td>Standard</td>
</tr>
<tr>
<td></td>
<td>(ms)</td>
<td>Deviation</td>
<td>(%)</td>
<td>Deviation</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>1374.9</td>
<td>411.5</td>
<td>61%</td>
<td>26%</td>
</tr>
<tr>
<td>P/AR</td>
<td>1312.6</td>
<td>222.6</td>
<td>69%</td>
<td>21%</td>
</tr>
<tr>
<td>FE</td>
<td>1298.9</td>
<td>289.4</td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td>Angry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>1603.9</td>
<td>337.6</td>
<td>66%</td>
<td>21%</td>
</tr>
<tr>
<td>P/AR</td>
<td>1609.2</td>
<td>213.4</td>
<td>72%</td>
<td>20%</td>
</tr>
<tr>
<td>FE</td>
<td>1768.5</td>
<td>221.6</td>
<td>58%</td>
<td>25%</td>
</tr>
<tr>
<td>Fearful</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>1605.4</td>
<td>291.4</td>
<td>63%</td>
<td>22%</td>
</tr>
<tr>
<td>P/AR</td>
<td>1509.3</td>
<td>268.9</td>
<td>68%</td>
<td>19%</td>
</tr>
<tr>
<td>FE</td>
<td>1676.4</td>
<td>227.4</td>
<td>54%</td>
<td>20%</td>
</tr>
<tr>
<td>Happy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>1494.1</td>
<td>297.9</td>
<td>71%</td>
<td>18%</td>
</tr>
<tr>
<td>P/AR</td>
<td>1453.7</td>
<td>185.2</td>
<td>71%</td>
<td>18%</td>
</tr>
<tr>
<td>FE</td>
<td>1663.5</td>
<td>359.0</td>
<td>65%</td>
<td>26%</td>
</tr>
</tbody>
</table>

NOTE: HC= Healthy controls (n=10), P/AR= Prodromal/ At risk (n=10), FE = First Episode (n=12), * = p<0.05
Table 8: Association between Emotional Distress and Brain Activation during the Emotional Face Identification

<table>
<thead>
<tr>
<th>Emotional Face Matching Task (Hariri)</th>
<th>Emotional Distress Pearson Correlation (r)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left MFG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angry</td>
<td>.45</td>
<td>.04*</td>
</tr>
<tr>
<td>Happy</td>
<td>-.02</td>
<td>.96</td>
</tr>
<tr>
<td>Right MFG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angry</td>
<td>-.11</td>
<td>.66</td>
</tr>
<tr>
<td>Happy</td>
<td>-.23</td>
<td>.32</td>
</tr>
</tbody>
</table>

NOTE: * = p<0.05;
Table 9: Association between Emotional Distress and Sleep Quality Indices measured by PSQI

<table>
<thead>
<tr>
<th></th>
<th>Emotional Distress</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson Correlation (r)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective Sleep Quality</td>
<td>.74</td>
<td>.001**</td>
<td></td>
</tr>
<tr>
<td>Sleep Latency</td>
<td>.71</td>
<td>.001***</td>
<td></td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>.62</td>
<td>.008**</td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>.25</td>
<td>.332</td>
<td></td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>.66</td>
<td>.004***</td>
<td></td>
</tr>
<tr>
<td>Use of Sleep Medication</td>
<td>.26</td>
<td>.310</td>
<td></td>
</tr>
<tr>
<td>Daytime Dysfunction</td>
<td>.57</td>
<td>.018*</td>
<td></td>
</tr>
<tr>
<td>PSQI Total</td>
<td>.82</td>
<td>.000**</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: * = p<0.05; ** = p<0.01;
Table 10: Summary Statistics for Clinical Variables in Low and High Activators

<table>
<thead>
<tr>
<th></th>
<th>Total BPRS</th>
<th>Global SAPS- Positive Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Low Activators (N=11)</td>
<td>18.6 (11.7)</td>
<td>7.3 (5.6)</td>
</tr>
<tr>
<td>High Activators (N=10)</td>
<td>10.9 (8.0)</td>
<td>3.2 (3.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>T</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Activators (N=11)</td>
<td>1.79</td>
<td>0.09*</td>
</tr>
<tr>
<td>High Activators (N=10)</td>
<td>2.04</td>
<td>0.057*</td>
</tr>
</tbody>
</table>

NOTE: + = Trend
Table 11: Regions of Activation during the Verbal Working Memory task when using Whole Brain Analyses

<table>
<thead>
<tr>
<th>Groups</th>
<th>Condition</th>
<th>Activation</th>
<th>Hemisphere</th>
<th>Region of Activation</th>
<th>Volume (in voxels)</th>
<th>Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC vs.</td>
<td>FE</td>
<td>Linear</td>
<td>3579</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC &gt; FE</td>
<td>L</td>
<td>Supramarginal Gyrus</td>
<td>40</td>
<td>31.4</td>
<td>55.1</td>
<td>19.6</td>
</tr>
<tr>
<td>HC &gt; FE</td>
<td>R</td>
<td>Middle Frontal Gyrus</td>
<td>34</td>
<td>32.6</td>
<td>28.2</td>
<td>27.8</td>
</tr>
<tr>
<td>HC &gt; FE</td>
<td>R</td>
<td>Right Superior Frontal Gyrus</td>
<td>34</td>
<td>22.8</td>
<td>-8.2</td>
<td>72.1</td>
</tr>
<tr>
<td>HC vs.</td>
<td>P/AR</td>
<td>Linear</td>
<td>3579</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC &gt; P/AR</td>
<td>L</td>
<td>Superior Temporal Gyrus</td>
<td>460</td>
<td>28.9</td>
<td>-9.1</td>
<td>6.7</td>
</tr>
<tr>
<td>HC &gt; P/AR</td>
<td>L</td>
<td>Cingulate Gyrus</td>
<td>114</td>
<td>-20</td>
<td>9.9</td>
<td>9.6</td>
</tr>
<tr>
<td>HC &gt; P/AR</td>
<td>R</td>
<td>Inferior Frontal Gyrus</td>
<td>91</td>
<td>37.9</td>
<td>40.3</td>
<td>16.7</td>
</tr>
<tr>
<td>HC &gt; P/AR</td>
<td>R</td>
<td>Medial Frontal Gyrus</td>
<td>71</td>
<td>-1.5</td>
<td>-8.7</td>
<td>48.1</td>
</tr>
<tr>
<td>HC &gt; P/AR</td>
<td>L</td>
<td>Postcentral Gyrus</td>
<td>51</td>
<td>54.9</td>
<td>35.2</td>
<td>43</td>
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<tr>
<td>HC &gt; P/AR</td>
<td>R</td>
<td>Medial Frontal Gyrus</td>
<td>50</td>
<td>-3.5</td>
<td>39.2</td>
<td>1</td>
</tr>
<tr>
<td>HC &gt; P/AR</td>
<td>R</td>
<td>Postcentral Gyrus</td>
<td>50</td>
<td>45.3</td>
<td>24.2</td>
<td>50</td>
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## Table Continued

<table>
<thead>
<tr>
<th>Groups</th>
<th>Condition</th>
<th>Activation</th>
<th>Hemisphere</th>
<th>Region of Activation</th>
<th>Volume (in voxels)</th>
<th>Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>P/AR</td>
<td>HC &gt; P/AR</td>
<td>R</td>
<td></td>
<td>Inferior Frontal Gyrus</td>
<td>41</td>
<td>43.7 0.5 27.4</td>
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<tr>
<td>P/AR</td>
<td>HC &gt; P/AR</td>
<td>R</td>
<td></td>
<td>Precuneus</td>
<td>32</td>
<td>-0.4 45.7 61.5</td>
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</table>
Table 12: Regions of Activation during the Emotional Face Matching (Hariri) task when using Whole Brain Analyses

<table>
<thead>
<tr>
<th>Groups</th>
<th>Condition</th>
<th>Activation</th>
<th>Hemisphere</th>
<th>Region of Activation</th>
<th>Volume (in voxels)</th>
<th>Coordinates</th>
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</thead>
<tbody>
<tr>
<td>HC vs.</td>
<td>P/AR</td>
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</tr>
<tr>
<td></td>
<td>Angry</td>
<td>HC &gt; P/AR</td>
<td>R</td>
<td>Superior Parietal Lobule</td>
<td>69</td>
<td>-19.7</td>
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<tr>
<td></td>
<td></td>
<td>HC &lt; P/AR</td>
<td>L</td>
<td>Fusiform Gyrus</td>
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<td>28.3</td>
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<td></td>
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<td>R</td>
<td>Middle Frontal Gyrus</td>
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<td>-21.4</td>
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<tr>
<td></td>
<td>Fearful</td>
<td>HC &gt; P/AR</td>
<td>R</td>
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<td>R</td>
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<tr>
<td></td>
<td>FE</td>
<td>FE &gt; HC</td>
<td>R</td>
<td>Cuneus</td>
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<td>-1.7</td>
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<td>R</td>
<td>Lingual Gyrus</td>
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<td></td>
<td>FE &gt; HC</td>
<td>R</td>
<td>Precuneus</td>
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<td></td>
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<td>R</td>
<td>Superior Temporal Gyrus</td>
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<td></td>
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<td>R</td>
<td>Parahippocampal Gyrus</td>
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<td>-29.8</td>
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<td></td>
<td>FE &gt; HC</td>
<td>L</td>
<td>Precuneus</td>
<td>2368</td>
<td>18.1</td>
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<td></td>
<td></td>
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<td>L</td>
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<td>R</td>
<td>Medial Frontal Gyrus</td>
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<td>-7.8</td>
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<td>Superior Frontal Gyrus</td>
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</tr>
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<td>P/AR</td>
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<td>R</td>
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<td>Caudate to Thalamus</td>
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<td>-0.6</td>
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<td>R</td>
<td>Precuneus</td>
<td>3968</td>
<td>-7.9</td>
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