Neurofunctional Characterization of the At-Risk Mental State for Psychosis

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
Neurobiology in the Graduate School
of Duke University

2014

ABSTRACT

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Abstract

Schizophrenia is a complex and debilitating psychiatric illness characterized by positive symptoms like hallucinations and delusions and negative symptoms like blunting of affect, avolition, and poverty of thought. This constellation of symptoms is hypothesized to result from dopaminergic dysfunction, glutamatergic dysfunction, and dysfunctional stress-reactivity. Prior to the onset of schizophrenia there is a prodromal period when individuals begin to experience sub-clinical symptoms and decreased functioning. This period is important to study not only to help elucidate biologic mechanisms of the illness but also to potentially alter the course of the illness through early treatment. The difficulty of studying this period lies in its recognizing it prospectively. To address this researchers have begun to study the at-risk mental state, a state that is associated with a high but not inevitable risk of conversion to psychosis. The studies described in this dissertation are aimed at a neurofunctional characterization of the at-risk mental state in three primary domains: reward-anticipation, hippocampus-dependent learning, and stress-reactivity. Individuals at-risk for psychosis and age-matched healthy volunteers underwent functional magnetic resonance imaging while performing tasks targeting these domains. In the reward-anticipation task, at-risk individuals showed decreased ventral tegmental area (VTA) and dorsolateral prefrontal cortex (DLPFC) responses to reward anticipation. In the hippocampus-dependent

learning task, at-risk individuals showed deficits in hippocampus-dependent memory, decreased VTA engagement, and increased DLPFC activation during learning of associations between items. In the stress-reactivity task, at-risk individuals showed increased activation in the bed nucleus of the stria terminalis/basal forebrain (BNST), anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC) in response to neutral faces. Collectively, these experiments show that neurofunctional deficits in reward-anticipation, hippocampus-dependent learning, and stress-reactivity are present in the putative prodrome, prior to the onset of psychosis. Regions implicated are those that would be expected based on current models of schizophrenia and neurofunctional studies in those with frank psychosis.

Dedication

For those affected by severe and persistent mental illness

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1. Introduction

1.1 Schizophrenia

Schizophrenia is a biologically complex and still not well-understood psychotic disorder defined by the presence positive symptoms, including delusions, hallucinations, disorganized thought processes, and negative symptoms, including blunting of affect, avolition, and poverty of thought, in addition to cognitive impairment(Mueser and McGurk, 2004). It is a severe and persistent mental illness that affects 1% of the population(Jablensky, 1997) and is associated with poor psychosocial functioning that is the primary burden on patients, their families, and society(Saleem et al., 2002). Its typical onset is between 18 and 25 years of age for men and between 26 and 45 years of age for women(Wyatt et al., 1988), with both environment and genetics contributing to its development. Multiple susceptibility genes have been identified in over 1000 genetic association studies. Most of the sixteen genes showing significant effects in a comprehensive metaanalysis(Allen et al., 2008) involve glutamatergic or dopaminergic neurotransmission. These susceptibility genes have low association strengths with the disorder and are thought to interact with environmental factors like obstetric complications associated with hypoxia(Cannon et al., 2002) and stressors like urbanicity(van Os et al., 2004) and migration(Cantor-Graae and Selten, 2005) to lead to the development of the illness.

1.2 Models of schizophrenia

The development of effective antipsychotic drugs (Delay et al., 1952) and subsequent inquiries into their mechanisms of action led to an interest in neurotransmitter-based hypotheses of schizophrenia. The classic and best-studied hypothesis was the dopamine hypothesis, which has undergone multiple revisions, with the most recent version highlighting dopaminergic dysregulation as the final common pathway in the development of schizophrenia(Howes and Kapur, 2009). Other abnormalities, including glutamatergic dysfunction and interactions between genetic and environmental factors are thought to funnel into this final common pathway. Separately, these abnormalities comprise the glutamatergic(Moghaddam and Javitt, 2011) and diathesis-stress(Walker and Diforio, 1997) models of psychosis. Together, the dopaminergic, glutamatergic, and diathesis-stress models characterize schizophrenia as a disorder of neurotransmitter dysregulation in the setting of a genetically and environmentally compromised brain.

1.2.1 Dopaminergic Model

The longest-studied model of schizophrenia highlights abnormalities in the dopaminergic system, thought to play a major role in schizophrenia pathogenesis(Lau et al., 2013). Formation of the dopamine hypothesis of schizophrenia began with the seminal 1963 discovery by Carlsson and Lindqvist that effective antipsychotic drugs accelerated dopamine metabolite formation, leading to the proposition that these major

antipsychotic drugs blocked dopamine receptors(Carlsson and Lindqvist, 1963). Further support for the hypothesis came with the evidence that drugs that enhanced dopaminergic neurotransmission could induce psychotic symptoms (Lieberman et al., 1987). The dopamine hypothesis became prominent in the 1970s, when clinical doses of antipsychotic drugs were found to block dopamine receptors, with clinical effectiveness directly related to their affinity for dopamine receptors(Seeman and Lee, 1975; Seeman et al., 1975; Creese et al., 1976). Because blockade of dopamine receptors improved symptoms of schizophrenia and drugs that enhanced dopaminergic neurotransmission worsened the symptoms of schizophrenia, hyperdopaminergia was thought to play a major role in the etiology of the disease(Snyder, 1976). Problems with the hypothesis that schizophrenia was a disease caused by excessive dopaminergic neurotransmission were evident. For example, dopamine antagonists were not effective at treating the negative symptoms of schizophrenia(Andreasen and Olsen, 1982), and dopamine metabolite levels were not consistently increased in the CSF (Widerlöv, 1988) of individuals with schizophrenia. In response to such findings, the theory that excess dopamine throughout the brain was the pathophysiological basis of schizophrenia was revised to reflect current ideas about regional specificity(Davis et al., 1991). Higher levels of dopamine and its metabolites were consistently found in the striatum in post-mortem brains of patients with schizophrenia than controls (Owen et al., 1978; Mackay et al., 1982; Toru et al., 1988). In addition, it was noted that the D2 receptors whose blockade

was so critical for the success of antipsychotic medications were prominent in the striatum, but had very low density in the prefrontal cortex, where D1 receptors predominated(Abi-Dargham and Moore, 2003). Together with findings that schizophrenia was associated with reduced frontal blood flow in PET studies that was correlated with low CSF dopamine metabolite levels, it was hypothesized that schizophrenia was associated with striatal hyperdopaminergia and prefrontal hypodopaminergia. The link between striatal hyperdopaminergia and prefrontal hypodopaminergia was made in animal studies focusing on dopamine neurons in the frontal cortex. Lesions of dopamine neuron terminals in the prefrontal cortex led to increased dopamine levels in the striatum(Pycock et al., 1980) and the injection of a dopamine agonist in the frontal cortex led to a reduction of dopamine metabolites in the striatum(Scatton et al., 1982). These findings gave Davis et al. a mechanism to suggest that frontal hypodopaminergia leading to striatal hyperdopaminergia might be characteristic of schizophrenia(Davis et al., 1991). In their revised hypothesis, Davis et al went even further to suggest that frontal hypodopaminergia might be associated with negative symptoms of schizophrenia based on commonalities between behaviors associated with frontal lobe lesions and the negative symptoms of schizophrenia. They also suggested that positive symptoms might be due to striatal hyperdopaminergia because of the effects of dopamine antagonists on these symptoms and the relationship

between higher dopamine metabolite levels and positive symptoms(Steinberg et al., 1993).

Research into the role of dopamine in schizophrenia proliferated after this landmark review. Increased presynaptic striatal dopamine availability was revealed with PET scanning of individuals with schizophrenia using radiolabelled L-Dopa(Hietala et al., 1995; 1999; Lindström et al., 1999; McGowan et al., 2004) with moderate to large effect sizes. Increased striatal dopamine release was demonstrated using PET and SPECT in multiple studies (Laruelle et al., 1996; Breier et al., 1997; Abi-Dargham et al., 1998), again with moderate to large effect sizes. In addition to providing this evidence for striatal hyperdopaminergia, these more recent studies have provided some additional support for prefrontal hypodopaminergia. Abi-Dargham et al. showed in two separate studies that d1 receptor density was increased in the prefrontal cortex in patients with schizophrenia (Abi-Dargham and Moore, 2003; Abi-Dargham et al., 2012), consistent with compensatory upregulation in response to chronic hypodopaminergia. Insufficient D1 receptor signaling in the prefrontal cortex has also been linked to negative symptoms and deficits in cognition in schizophrenia (Goldman-Rakic et al., 2004; Tamminga, 2006).

While some of the studies described so far have shown links between dopaminergic dysfunction and clinical symptoms, they have not addressed the question of how dopaminergic dysfunction could lead to the clinical symptoms. Dopaminergic

signaling is involved in the coding of incentive salience(Berridge and Robinson, 1998) and reward prediction(Schultz et al., 1997). In the brains of individuals with schizophrenia, the excessive firing of dopaminergic neurons leading to the excessive release of dopamine may lead to an aberrant assignment of salience to neutral internal and external stimuli. This misattribution of salience to unimportant items may then, when experienced by individuals with different sets of cognitive and social experiences, lead to different delusions and hallucinations in different people (Kapur, 2003). Indiscriminate firing of dopamine neurons may also lead to the negative symptoms of schizophrenia by making it difficult or impossible to distinguish the signal from the noise regarding stimuli that do and do not indicate reward. This idea is both described and supported in a study by Roiser et. al that shows an association of the aberrant assignment of salience with negative symptoms(Roiser et al., 2009) The lack of items to incite motivation could arguably lead to avolition, anhedonia, social withdrawal, and ultimately, decreased psychosocial functioning.

1.2.2 Glutamatergic Model

While the dopamine hypothesis of schizophrenia is the most prominent and well-studied explanation for the pathophysiology of schizophrenia, recent interest has been devoted to the glutamate hypothesis(Coyle, 2006; Moghaddam and Javitt, 2011), which is becoming increasingly popular as a supplementary model. The glutamate hypothesis posits that schizophrenia is a disease of glutamatergic dysfunction caused by

reduced function of N-methyl-D-aspartate (NMDA) glutamate receptors(Coyle, 2006). Like the dopamine hypothesis, original interest in the glutamate hypothesis began due to effects of pharmacological agents on behavior. Ketamine and phencyclidine (PCP) are antagonists of the NMDA receptor(Javitt and Zukin, 1991), and administration of either mimics symptoms of schizophrenia, including hallucinations, delusions, thought disorganization, and negative symptoms in healthy subjects (Luby et al., 1959; Krystal et al., 1994) In chronic, stable subjects with established schizophrenia, administration reintroduces a clinical picture consistent with the acute stage of illness (Luby et al., 1959). Administration of these NMDA antagonists was first shown to lead to increases in glutatamate in the prefrontal cortex in rodents using microdialysis(Moghaddam et al., 1997). This was followed by work in humans using magnetic resonance spectroscopy that could measure glutamine, a marker of glutamate turnover, that showed increases in the anterior cingulate cortex (ACC) after ketamine administration(Rowland et al., 2005). Glutamine levels were also increased in the ACC and thalamus of patients with schizophrenia(Théberge et al., 2002).

The pathophysiological basis of schizophrenia is attributed to NMDA hypofunction by proponents of this theory for the following reasons. First, the symptoms match those elicited by NMDA antagonists as previously described. Second, mismatch negativity, a potential that is caused by current through NMDA channels(Javitt et al., 1996), is reduced in schizophrenia(Shelley et al., 1991) and in

normal subjects treated with ketamine(Umbricht et al., 2000). In addition, psychosis related to autoimmune disorders is associated with anti-NMDA receptor antibodies(Omdal et al., 2005), providing natural and unexpected support for the theory that NMDA hypofunction may lead to psychotic symptoms.

Multiple different mechanisms could lead to NMDA hypofunction in schizophrenia. NR2A and NR2B mutations are both associated with schizophrenia(Qin et al., 2005; Martucci et al., 2006). In addition, NR2A subunits on neurons in the ACC are decreased in number in schizophrenia(Woo et al., 2004), suggesting that direct dysfunction in NMDA receptors may contribute to schizophrenia. Mutations in G72, a gene that encodes a protein that activates the enzyme that catabolizes D-serine, a coagonist for NMDA receptors, have been associated with schizophrenia in multiple studies(Chumakov et al., 2002; Addington et al., 2004; Korostishevsky et al., 2004). Serum and CSF levels of d-serine have also been shown to be decreased in patients with schizophrenia(Hashimoto et al., 2003; 2005), and improvement in symptoms is noted with replacement(Heresco-Levy et al., 2002). Multiple other susceptibility genes for schizophrenia involve NMDA receptor signaling, including neuregulin1(Harrison and Owen, 2003), dysbindin(Straub et al., 2002), RGS4(Chowdari et al., 2002), PPP3CC(Gerber et al., 2003), and the NRI subunit gene GRIN1(Martucci et al., 2003). These complex genetic factors are thought to work through the alteration of NMDA receptor function to result in a similar clinical syndrome across populations.

While the dopaminergic and glutamatergic models of schizophrenia are the most accepted and widely studied neurotransmitter models, abnormalities in most other neurotransmitter systems, including GABA, serotonin, and acetylcholine have also been demonstrated. A full explanation of the neurotransmitter dysfunction in schizophrenia is beyond the scope of this dissertation; however, the data presented here can contribute to a synthesis of major neurotransmitter abnormalities in schizophrenia, as argued in the final chapter..

1.2.3 Diathesis-stress Model

In concert with the neurotransmitter-based models of schizophrenia, the diathesis-stress model provides important insights into the pathophysiological basis for schizophrenia. Diathesis-stress models of schizophrenia theorize that psychosocial stress contributes to the development of schizophrenia in individuals who have a predisposition towards the illness (Nuechterlein and Dawson, 1984; Walker and Diforio, 1997). This predisposition, or diathesis, may be described psychologically or biologically, but most modern descriptions focus on either a genetic predisposition or a biological predisposition secondary to hypothalamic-pituitary-adrenal (HPA) axis, hippocampal, and dopaminergic dysfunction(Walker and Diforio, 1997; Corcoran et al., 2003; van Winkel et al., 2008).

Psychosocial stress can precipitate(DeVylder et al., 2012) or worsen(Norman and Malla, 1994) psychotic symptoms in vulnerable individuals. Risk for psychosis increases

with the number of traumatic experiences an individual has (Shevlin et al., 2008), and risk for psychosis has been associated with multiple different stress-associated environmental factors, including urbanicity(van Os et al., 2004), migration(Cantor-Graae and Selten, 2005), and discrimination(Veling et al., 2007). Even more important than the actual life experiences seems to be the stress response evoked by them. Patients with psychosis exhibit increased reactivity to daily life stressors(Myin-Germeys et al., 2001), and impaired stress tolerance predicted conversion to psychosis better than severity of attenuated psychotic symptoms in such individuals(Yung et al., 2005). Impaired stress tolerance in at-risk individuals is also associated with an increase in positive and negative symptoms over time(DeVylder et al., 2012).

In line with these findings, recent versions of the diathesis-stress model of schizophrenia consider hyperactivity of the HPA axis a biological vulnerability that predisposes individuals to developing schizophrenia when exposed to stressors (Walker and Diforio, 1997; Corcoran et al., 2003; Myin-Germeys and van Os, 2007). Consistent with HPA axis hyperactivity, cortisol and ACTH levels are increased at baseline in individuals with schizophrenia(Ryan et al., 2004), and these individuals have excessive increases in ACTH in response to a metabolic challenge(Elman et al., 1998). In addition, cortisol secretion in at-risk individuals shows a strong relationship with positive symptoms(Walker et al., 2001) and the ability to predict transition to psychosis(Walker et al., 2010). Increased HPA axis responsivity to stress is thought to lead to a cascade of

events leading to circuit dysfunction, with the final result being dysfunctional dopaminergic signaling(Walker and Diforio, 1997). These changes are described in detail in conjunction with the dopaminergic and glutamatergic models in the following section.

1.2.4 Circuit-Based Integrated Model

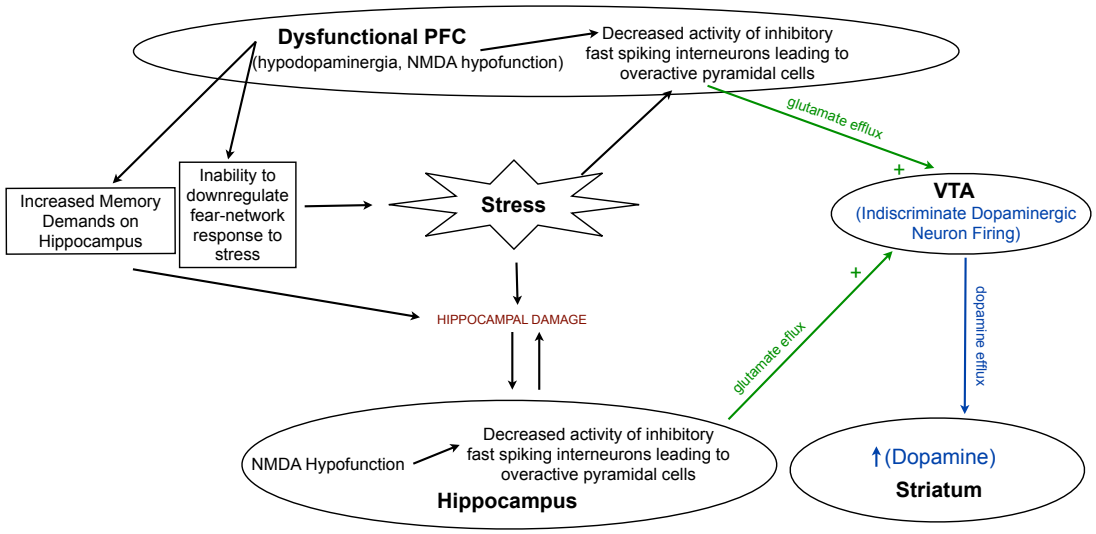

Figure 1. Circuit-based integrated model of schizophrenia.
This model draws from the dopaminergic, glutamatergic, and diathesis-stress models of schizophrenia development.

The dopaminergic, glutamatergic, and diathesis-stress models of schizophrenia can be integrated with a circuit-based approach that can provide a scaffolding for integrating findings relevant for understanding the development of schizophrenia (Figure 1). An obvious link between the dopaminergic and glutamatergic hypotheses was revealed by mimicking NMDA receptor hypofunction with ketamine administration and showing a concomitant increase in striatal dopamine(Vollenweider

et al., 2000). A potential explanation for this increase involves a string of events that begins with NMDA receptor inhibition leading to a reduction in excitation of fast-spiking typically inhibitory interneurons. Decreased activity of the fast-spiking interneurons in the hippocampus enhances dopamine release from the ventral tegmental area (VTA) that can be reversed by inactivating the hippocampal subiculum(Lodge and Grace, 2007). Decreased inhibition of fast-spiking neurons also leads to overactive pyramidal cells, particularly in the hippocampus, which has detrimental effects on these cells(Olney and Farber, 1995), and provides a partial explanation for two of the most prominent and robust findings in schizophrenia, decreased hippocampal volume(Adriano et al., 2012) and associated dysfunction(Heckers and Konradi, 2010). The other most prominent and replicated finding in schizophrenia is increased striatal dopaminergic activity(Reith et al., 1994; Dao-Castellana et al., 1997; Hietala et al., 1999; Howes et al., 2007) and hippocampal and dopaminergic dysfunction can be linked in a cohesive explanation for the pathophysiology of schizophrenia. The hippocampus is critically involved in regulation of dopaminergic neuron activity in the VTA(Lisman and Grace, 2005) and activation of dopamine receptors in the hippocampus is critical for the persistence of hippocampus-dependent memory(Bethus et al., 2010). Hippocampal dysfunction may lead to dysregulation of the dopaminergic system, with a disruption of regulation of the subiculum leading to hyperdopaminergia in the striatum secondary to

aberrant activation of dopaminergic neurons in the dopaminergic midbrain (Lodge and Grace, 2007; Lisman et al., 2008; Grace, 2010).

With hippocampal dysfunction leading to dopaminergic overdrive understood as one mechanism for striatal hyperdopaminergia in schizophrenia, the question of what outside factor might lead to the hippocampal dysfunction still remains. In a recent review, Anthony Grace suggests that stress may be the cause of hippocampal dysfunction in schizophrenia(Grace, 2012). Constant stress leads to hippocampal damage (Magariños and McEwen, 1995; McEwen, 2000; Sapolsky, 2000) and individuals with schizophrenia have increased responsivity to daily stressors(Myin-Germeys et al., 2001) and increased HPA axis activation(Elman et al., 1998; Ryan et al., 2004). The increased response to stressors in schizophrenia could be secondary to decreased ability of the prefrontal cortex to regulate stress as suggested by prefrontal dysfunction in other domains(Grace, 2012). Consistent with this idea, loss of prefrontal cortical dopamine increases striatal dopamine release in response to stressors(Deutch et al., 1990; King et al., 1997). If the prefrontal cortex could not effectively regulate stress responses, the resulting uncontrolled responses could lead to hippocampal dysfunction and hyperdopaminergia characteristic of psychosis. Prefrontal dysfunction could lead to hyperdopaminergia through a direct mechanism as well, with increased glutamatergic neurotransmission in response to stressors leading to increased dopaminergic neurotransmission from the VTA(Moghaddam, 2002)

1.3 Neurofunctional abnormalities in schizophrenia consistent with the integrated model

Functional imaging investigations using cognitive and affective neuroscience paradigms allow for the study of brain system abnormalities that underlie deficits in cognition and affect in schizophrenia(Gur and Gur, 2010). Neuroimaging studies can noninvasively address the hypothesis that neuronal functions associated with dopaminergic and glutamatergic signaling are altered in schizophrenia. As would be predicted based on the dopaminergic, glutamatergic, and diathesis-stress models of schizophrenia, individuals with schizophrenia exhibit prominent neurofunctional deficits in paradigms addressing functions that rely heavily on dopaminergic and glutamatergic neurotransmission and contribute to or are impaired by increased stress-reactivity. Three prominently relevant regions include the prefrontal cortex, striatum, and hippocampus.

1.3.1 Prefrontal Cortex

Individuals with schizophrenia have deficits in multiple domains of motivational and cognitive functioning, and it is argued that these deficits can be traced to impairments in the dorsolateral prefrontal cortex (DLPFC) and its interactions with other regions(Barch and Ceaser, 2012). The studies that support this argument are consistent with the dopaminergic model of schizophrenia that posits frontal hypodopaminergia in schizophrenia. Executive control has been well-studied using fMRI in schizophrenia, with a meta-analysis of 41 imaging studies of executive

functioning showing reduced activation of the DLPFC in schizophrenic patients(Minzenberg et al., 2009). Working memory is another commonly studied cognitive domain that has shown clear evidence for hypoactivation of the DLPFC. This was first demonstrated with the Wisconsin Card Sorting task(Weinberger et al., 1986), but that has also been demonstrated in other tests of working memory, including the Tower of London (Andreasen et al., 1992), verbal fluency(Yurgelun-Todd et al., 1996), and the n-back task(Carter et al., 1998). A meta-analysis of studies comparing brain activation in schizophrenic patients relative to controls in the n-back task, a prototypical working memory paradigm(Glahn et al., 2005), showed robust support for DLPFC hypoactivation during working memory in schizophrenia. Prefrontal dysfunction has recently also been shown in relation to relational memory deficits in schizophrenia. The original focus in fMRI studies of these deficits in memory in schizophrenia was the temporal lobe, primarily the hippocampus, which has long been implicated in the encoding, binding, and retrieval of information(Eichenbaum et al., 2007; Konkel and Cohen, 2009). Recent work has shown that the DLPFC contributes to relational memory formation(Murray and Ranganath, 2007; Blumenfeld et al., 2011), and, consistent with this finding, Ragland et al have recently shown DLPFC activation deficits for schizophrenic patients during relational encoding(Ragland et al., 2012). A meta-analysis of functional deficits during episodic memory in schizophrenia also revealed activation deficits in the DLPFC(Ragland et al., 2009).

1.3.2 Striatum

While fMRI studies of cognitive domains such as executive control, working memory, and episodic memory implicate DLPFC hypoactivation consistent with prefrontal hypodopaminergia described in the region-specific dopamine hypothesis of schizophrenia(Davis et al., 1991), studies of many aspects of reward processing provide evidence for the striatal dysfunction described in the same hypothesis. Juckel et al. showed that individuals with schizophrenia exhibit impaired activation of the ventral striatum, a central region of the dopaminergic reward system, in response to the prediction of stimuli that predicted monetary gain(Juckel et al., 2006). Because fMRI is contrast based, this provides support for the idea of aberrant salience. In models of aberrant salience, dopaminergic dysregulation leads to increased noise in the system that can prevent dopaminergic signals linked to stimuli indicating reward from being detected(Roiser et al., 2009). If schizophrenic individuals engaged the striatum for all stimuli, including those that did not predict monetary gain, there would be reduced contrast-based activation to reward, as was seen in Juckel's study(Juckel et al., 2006) and a subsequent study that used a similar task to study reward anticipation in patients with schizophrenia versus controls(Nielsen et al., 2012) . Interestingly, the less ventral striatal activation to reward predicting stimuli that schizophrenic patients had, the more negative symptoms they exhibited(Juckel et al., 2006). This provides support for the idea from incentive salience models that the increased noise in the system could "drown

out" motivational signals, leading to negative symptoms like avolition and decreases in psychosocial function caused by lack of interest and social withdrawal(Howes and Kapur, 2009). Further support was provided in a study of prediction-error related activation to primary reinforcers in schizophrenia patients vs controls(Waltz et al., 2008). In this study, patients with schizophrenia showed attenuated responses to positive reward prediction errors (unexpected juice rewards) compared to controls, but they showed no deficits in activation to negative reward prediction errors (unexpected juice omissions). Patients with schizophrenia also showed decreased activation in many areas, including midbrain and striatum, in response to any juice delivery, including delivery that was predicted. Activation in the striatum and gustatory cortex evoked by such juice delivery was significantly negatively correlated with clinical ratings of avolition in these patients, such that the patients with the least BOLD response in these regions to juice rewards showed the highest avolition ratings. Individuals with schizophrenia also showed decreased prediction-error related responses in the midbrain and striatum to a secondary financial reinforcer in a similar study(Murray et al., 2008).

1.3.3 Hippocampus

The hippocampus is a key region for integrating the dopaminergic, glutamatergic and stress diathesis models of psychosis, and hippocampal dysfunction has been consistently demonstrated in functional imaging studies. Less hippocampal activation has been demonstrated in patients than controls in various hippocampus

dependent tasks, including episodic encoding(Jessen et al., 2003), relational memory formation(Ongür et al., 2006), word and face recognition(Rametti et al., 2009), novelty recognition(Weiss et al., 2004), and, most recently, virtual navigation(Ledoux et al., 2013). The decreased activation seen in these studies could be secondary to decreased engagement of the hippocampus for stimuli of interest or to increased engagement at baseline for all stimuli. There are two lines of evidence in favor of the second interpretation. First, patients with schizophrenia were shown to display hippocampal hyperactivity with deep encoding irrespective of encoding success (Zierhut et al., 2010). Second, and more convincing, are findings in two different studies that the hippocampus does not habituate to repeated face presentations in schizophrenia(Holt et al., 2006; Williams et al., 2013). Lack of discriminability in hippocampal activation for old and new stimuli was correlated with decreased memory performance in schizophrenia, suggesting the decreased ability of the hippocampus to habituate might contribute to the memory deficits in the disorder(Williams et al., 2013). The hippocampal dysfunction demonstrated in these studies is consistent with the integrated circuit model described previously, which suggests strong contributions of hippocampal dysfunction to dopaminergic dysfunction in schizophrenia. The interpretation that there is increased activity at baseline with decreased recruitment for hippocampus-dependent tasks(Heckers and Konradi, 2010) is in line with evidence provided in a recent combined human and animal imaging study that initial hippocampal overdrive leads to

hippocampal atrophy in schizophrenia(Schobel et al., 2013). This study first showed hippocampal hypermetabolism was present in the CA1 region with spread to the subiculum. This was then shown to predict atrophy in the hippocampus that was most prominent in these regions. In parallel experiments, ketamine was used to model psychosis in mice, which produced hypermetabolism in similar regions immediately and after repeated exposure, which also led to atrophy. Using direct measurements of extracellular glutamate, glutamate was shown to drive these neuroimaging changes. Taken together the findings from this experiment provide a mechanism for some of the glutamate-induced pathology in schizophrenia, with glutamate-driven hippocampal hypermetabolism leading to hippocampal atrophy characteristic of the disorder(Schobel et al., 2013).

1.4 At-risk mental state for psychosis

Prior to the onset of schizophrenia there is a prodromal period when individuals begin to experience sub-clinical symptoms and decreased functioning(Yung et al., 2005). The difficulty of studying this period lies in its recognizing it prospectively. To address this researchers have begun to study the at-risk mental state, a state that is associated with a high but not inevitable risk of conversion to psychosis in individuals who experience subthreshold symptoms of psychosis (Yung et al., 2012). While the at-risk mental state technically refers to a mental state that is putatively prodromal for any psychotic disorder, the most common and most commonly studied psychotic disorder is

schizophrenia, thus these terms are often used interchangeably in common practice and in this dissertation. Different interview measures have been developed to assess ultra high risk (UHR) criteria to determine which individuals might be at high risk for developing psychosis. These include the Comprehensive Assessment of At-Risk Mental States (CAARMS)(Yung et al., 2005), the Structured Interview for Prodromal Symptoms(Miller et al., 2003), and the Bonn Scale for the Assessment of Basic Symptoms(Vollmer-Larsen et al., 2007). A recent meta-analysis quantified the increased risk associated with being labeled as at UHR based on these criteria, showing a transition rate of 18% at six months, 22% at one year, 29% at two years, and 36% at three years(Fusar-Poli et al., 2012). While these instruments attempt to prospectively identify the prodrome, the mental state it identifies is not necessarily prodromal, as not everyone who is identified goes on to develop a psychotic disorder. Thus the mental state of those identified by these instruments is thus termed the at-risk mental state (ARMS), as it confers increased but not 100% risk of development of a psychotic disorder in the near future.

Studying the at-risk mental state is important for understanding the schizophrenia, as abnormalities may be identified in the at-risk mental state that could play a critical role in its pathogenesis. Individuals during this putatively prodromal phase have not yet experienced long term treatment with antipsychotics, institutionalization, or neurodegeneration that is characteristic of chronic disease, thus

allowing research into mechanisms underlying the disease while avoiding common confounds. It is also important to study as interventions in individuals in this putative prodrome may prevent or delay progression to psychosis(McGorry et al., 2009). At the very least, interventions initiated during this period would shorten the duration of untreated illness, which has been shown to improve functional outcome in individuals with schizophrenia(Tang et al., 2014).

1.5 Neuroimaging findings in the at-risk mental state consistent with the integrated model

Functional and neurochemical imaging are powerful tools for studying the brain dysfunction present during the at-risk mental state, prior to the onset of the disorder. They allow the opportunity for neurofunctional and neurochemical characterizations of the at-risk mental state in addition to the potential identification of neurobiological and neurochemical vulnerability markers for the development of schizophrenia.

1.5.1 Neurochemical Findings

In neurochemical imaging studies conducted thus far focusing on the at-risk mental state, findings have generally been qualitatively similar to those in established disease, but less severe. For example, striatal dopaminergic overactivity (increased striatal [18F]-dopa uptake) was demonstrated in individuals with prodromal symptoms(Howes et al., 2009), which approached levels seen in individuals with established schizophrenia. Uptake was correlated with symptom severity as assessed using both the PANSS and CAARMS in at-risk individuals, consistent with the

hypothesized role of dopaminergic dysfunction in the pathophysiology of schizophrenia. Glutamine was also shown to be increased in the ACC in at-risk individuals(Stone et al., 2009), consistent with findings in individuals with schizophrenia and with the glutamate hypothesis of schizophrenia pathophysiology.

1.5.2 Neurofunctional Findings

As with neurochemical imaging, fMRI study results have revealed dysfunction in regions implicated in established disease. fMRI studies in the at-risk mental state are a relatively new undertaking, with the first being conducted in 2005(Morey et al., 2005) showing decreased target-related prefrontal activation in clinical high risk individuals compared with controls when performing an executive function task. As expected based on neural circuit abnormalities predicted by dopaminergic and glutamatergic hypotheses of schizophrenia and fMRI findings in established disease, such prefrontal hypoactivation was common throughout subsequent studies in at-risk individuals performing various tasks. A recent metaanalysis of fMRI studies in at-risk individuals(Fusar-Poli, 2012) showed reduced activation in the left inferior frontal gyrus, superior frontal gyrus, and ACC. No additional clusters of reduced or increased activation were found. All fMRI studies that compared a clinical high risk group and control group using whole-brain fMRI methods were included, regardless of the specific task design, and reduced prefrontal activation was found consistently. Decreased prefrontal activation has been seen in some working memory studies completed after

this metaanalysis(Broome et al., 2010a; Fusar-Poli et al., 2010b), but increased prefrontal activation, particularly in the medial and inferior prefrontal cortex but also in the DLPFC has been demonstrated in others(Broome et al., 2010b; Fusar-Poli et al., 2011; Yaakub et al., 2013). Studies outside of the prefrontal cortex in at-risk individuals have been more sparse. Striatal dysfunction has also demonstrated in the at-risk mental state, although far less robustly than in established illness, with decreased NAcc activation during the anticipation of loss avoidance being found at trend-level in at-risk individuals(Juckel et al., 2012). As in individuals with established disease, altered medial temporal cortex function has been demonstrated in at-risk individuals during memory encoding and retrieval and associated with decreased recognition performance(Allen et al., 2011). Medial temporal lobe abnormalities were also demonstrated during emotional discrimination involving neutral face stimuli in at-risk individuals, in addition to prefrontal cortex, cuneus, and thalamus(Seiferth et al., 2008).

1.5.3 Combined Neurochemical and Neurofunctional Findings

Combined fMRI-PET studies have provided further evidence for circuit based abnormalities predicted by dopaminergic and glutamatergic hypotheses of schizophrenia. In a combined [18F]-dopa PET-fMRI study, increased dopamine function was confirmed in the striatum of at-risk individuals and shown to be negatively correlated with prefrontal cortex activation during the classic n-back working memory task, whereas striatal dopamine function was positively correlated with prefrontal

activation during this task in healthy individuals(Fusar-Poli et al., 2010b). These findings are consistent with a prominent model of schizophrenia in which striatal dopaminergic overactivity is thought to result from reduced activity in the prefrontal cortex(Moore et al., 1999). Because previous neuroimaging studies had implicated dopaminergic dysfunction(Howes et al., 2009)in the at-risk mental state and medial temporal lobe dysfunction (Allen et al., 2011) during an episodic memory task in the at-risk mental state, another fMRI-PET study of at-risk individuals was conducted in which these findings were extended by showing that the at-risk mental state was associated with an altered relationship between MTL activation and striatal dopamine function(Allen et al., 2012), consistent with Lisman and Grace's model that striatal hyperdopaminergia is driven by MTL dysfunction(Lisman et al., 2008). Imaging is of great interest in this population as all of them do not eventually develop schizophrenia, providing the opportunity for imaging to facilitate the targeting of abnormalities that predict which of them will.

1.6 Experimental aims and rationale

The few neurofunctional studies conducted so far provide evidence that some of the abnormalities seen in frank schizophrenia are paralleled by those in the at-risk mental state, but they cover few cognitive domains and have small sample sizes(Fusar-Poli, 2012). Much work remains to be done to characterize the functional deficits present

before the onset of frank psychosis that could represent neurofunctional correlates of vulnerability.

To better characterize neurofunctional abnormalities in the at-risk mental state, three different cognitive activation paradigms were administered to a large cohort of at-risk individuals and control individuals during fMRI scanning. These paradigms were specifically chosen to assess components of cognition and affect that might put young people at highest risk for psychosis. They systematically targeted interacting motivational and memory systems including reward prediction and hippocampus-dependent learning in addition to affective biases, all areas with known dysfunction in schizophrenia and associated with prominent models of the disease.

Chapter 2 presents an experiment designed to highlight reward-system abnormalities in the at-risk mental state consistent with the dopaminergic hypothesis of schizophrenia. Participants see and respond to cues predicting reward while neurofunctional activation associated with the anticipation of reward is assessed. Chapter 3 presents an experiment designed to highlight dopaminergic system dysfunction during associative learning and generalization. The task participants complete during scanning involves making connections between faces and scenes and generalizing that knowledge to new stimuli. Chapter 4 presents an experiment focused on stress reactivity in the at-risk mental state. Human faces with fearful and neutral

expressions are used as stimuli to engage fear and threat-related regions, with a focus on abnormalities in neurofunctional responses in at-risk individuals.

Together, these studies aim to provide a neurofunctional characterization of the at-risk mental state that is consistent with an integrated circuit-based model that incorporates principles from the prominent dopaminergic, glutamatergic, and stress-diathesis models of schizophrenia.

2. Decreased dopaminergic midbrain engagement during reward-anticipation in individuals at risk for psychosis

2.1 Introduction

Schizophrenia is associated with prominent deficits in multiple aspects of reward processing, including neural responses to reward anticipation(Juckel et al., 2006), reward receipt(Waltz et al., 2010), and reward prediction errors(Murray et al., 2008; Waltz et al., 2008), in addition to deficits in translating affective reward experience into action(Heerey and Gold, 2007). Such deficits are revealed clinically in the avolition, anhedonia, social withdrawal(Mueser and McGurk, 2004), and ultimately, decreased psychosocial functioning(Hunter and Barry, 2012) experienced by patients who suffer from the disease.

Many of these symptoms begin to emerge prior to the onset of the illness in a putatively prodromal period termed the at-risk mental state for psychosis(Yung et al., 2005). This state, characterized by subclinical symptoms and associated with increased but not inevitable risk of transition to psychosis, has received increasing attention over the last twenty years(Fusar-Poli et al., 2013), with the first fMRI study completed less than 10 years ago (Morey et al., 2005) focusing on fronto-striatal function in an executive function task.

Despite the known reward-system dysfunction in schizophrenia, there has been only one previous fMRI study of reward-processing in the at-risk mental state(Juckel et

al., 2012). This study was based on a prior study of reward-anticipation in individuals with established schizophrenia(Juckel et al., 2006), in which Juckel et al. showed that individuals with schizophrenia exhibit impaired activation of the ventral striatum, a central region of the dopaminergic reward system, in response to the prediction of stimuli that predicted monetary gain(Juckel et al., 2006). Because fMRI is contrast based, this finding provided support for the idea of aberrant salience. In models of aberrant salience, dopaminergic dysregulation leads to increased noise in the system that can prevent dopaminergic signals linked to stimuli indicating reward from being detected(Roiser et al., 2009). If schizophrenic individuals engaged the striatum for all stimuli, including those that did not predict monetary gain, there would be reduced contrast-based activation to reward. This was demonstrated in both Juckel's original study (Juckel et al., 2006) and a similar study of reward anticipation in patients with schizophrenia versus controls(Nielsen et al., 2012).

To determine if early reward-system dysfunction could be demonstrated in the putatively prodromal phase of schizophrenia development, Juckel et al. performed a follow-up fMRI study to assess ventral striatal responses to reward-anticipation and anticipation of loss-avoidance in the at-risk mental state. They were able to demonstrate similar deficits in reward-system recruitment but only for the anticipation of loss-avoidance and only at trend-level for at-risk individuals vs controls. One potential reasons their findings were not robust is their sample size was small, with only 13

individuals in each group(Juckel et al., 2012), a common limitation of fMRI studies targeting clinically at-risk individuals(Fusar-Poli, 2012). They also only focused on one central region of the dopaminergic reward system, the ventral striatum, rather than including analyses of the origin of mesolimbic dopaminergic neurons, the VTA. To determine if further support could be provided for the hypothesis that deficits in reward-anticipation are present during the at-risk mental state, we conducted a larger study including data from 60 at-risk individuals, with analyses including this important reward-related region of interest.

In this study of reward-system dysfunction in the at-risk mental state, we used functional magnetic resonance imaging (fMRI) in individuals at-risk for developing psychotic disorders and healthy individuals as they anticipated reward and loss-avoidance. We hypothesized that individuals at risk for psychosis would show a reduction in activation in regions associated with reward processing including the prefrontal cortex, nucleus accumbens, and VTA in response to anticipation of reward or of loss-avoidance.

2.2 Methods

2.2.1 Participants

Sixty-nine at-risk and 40 healthy control volunteers between 14 and 29 years of age participated. Help-seeking participants were recruited from the Longitudinal Youth At-Risk Study (LYRIKS) through Singapore Institute of Mental Health clinics, armed

forces, and community mental health services. The at-risk group was identified using the Comprehensive Assessment of At-Risk Mental States (CAARMS)(Yung et al., 2005). Healthy control participants were recruited through public advertisements in print, social and online media and were matched for age with at-risk participants. Participants were excluded for current substance abuse or a history of serious medical or neuropsychiatric disorders, including mental retardation. Nine at-risk participants and three controls were excluded for excessive head motion (rotation > 2 degrees, absolute displacement > 3 mm, or relative displacement > 1 mm). One at-risk participant was excluded due to an incidental brain finding. In total, data from 60 at-risk and 37 control participants were included. Thirty-three of the included at-risk participants were taking antidepressant medications (selective serotonin reuptake inhibitors [n=27]; tricyclic or tetracyclic antidepressants [n=3]; combination of antidepressant subtypes [n=3]). Two included participants were taking low-dose antipsychotics (one on quetiapine, one on chlorpromazine).

Both at-risk and control participants completed a battery of neurocognitive tests assessing a range of functions, including working memory, attention, vigilance, and a standard IQ proxy, the Wechsler Abbreviated Scale of Intelligence Vocabulary Subtest (The Psychological Corporation, 1999). At-risk participants were assessed using the Positive and Negative Syndrome Scale (PANSS)(Kay, 1990), Brief Assessment of Cognition in Schizophrenia(Keefe et al., 2004), and Global Assessment of Functioning

(GAF) scale (DSM-IV-TR, p. 34). Because left-handedness is more common in schizophrenia, we did not attempt to balance the groups, to avoid introducing bias; however, analyses included handedness (assessed using an inventory(Annett, 1967)) as a covariate.

Permission to enroll participants was obtained from the Singapore National Healthcare Group Domain Specific Review Board. Participants over 21 gave written informed consent after a full study description. Participants under 21 gave assent to written consent obtained from their parent or guardian.

2.2.2 Task

The task used in this experiment is a version of the monetary incentive delay (MID) task(Knutson et al., 2001) in which images of Singaporean currency are used instead of abstract cues (Figure 2). This substitution was made to decrease cognitive demands in this impaired population. During each trial, a cue (gain $0, gain $1, gain $5, lose $0, lose $1, lose $5, or a neutral $0 cue) was presented for 500 ms, indicating the amount at stake for that trial. After a variable delay of 2-2.5 seconds, a white square target appeared on the screen. Subjects responded with a button press with the index finger of their dominant hand as quickly as possible, before the target left the screen. Within gain-anticipation trials, responses that were sufficiently fast resulted in additions to the subject's bank in the amount indicated by the cue and responses that fell outside of the accepted window resulted in no change to the subject's bank. Within loss

avoidance trials, responses that were sufficiently fast resulted in no change to the subject's bank and responses that fell outside of the accepted window resulted in a loss of the amount indicated by the cue. Difficulty was individually titrated after a practice/calibration run to approximate a 66% hit rate by adjusting the response time window for hit responses using an adaptive algorithm. Independent thresholds were used for each trial type. After each target, a feedback screen appeared for 1.5 seconds and displayed the results of the trial (gain, loss, or no change) and the cumulative total. Participants completed two runs of 70 trials each, with 10 trials per condition.

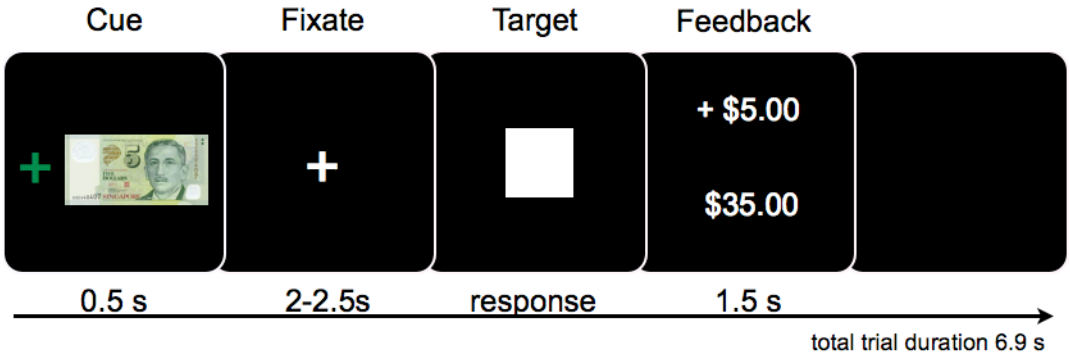

Figure 2: Monetary incentive delay task design.
Participants see a cue indicating the amount at stake. They must respond to the target quickly enough to win or avoid losing.

A hippocampus-dependent learning task(Shohamy and Wagner, 2008), emotional face processing task(Hall et al., 2008)and working memory paradigm(Chee and Choo, 2004) were administered in the same session as this task. We have previously reported findings from the working memory paradigm(Yaakub et al., 2013), findings

from the hippocampus-dependent learning task and emotional face processing task appear in later chapters of this dissertation.

2.2.3 Behavioral data analysis

Response times for gain trials were submitted to a 3 condition (gain $0 versus gain $1 versus gain $5; within-subjects) x 2 group (at-risk versus control; between subjects) repeated measures analysis of variance (ANOVA). Response times for loss trials were also submitted a 3 condition (lose $0 versus lose $1 versus lose $5; within-subjects) x 2 group (at-risk versus control; between subjects) repeated measures ANOVA. P-values less than 0.05 were considered significant. When the sphericity assumption was violated, Greenhouse-Geisser corrected values were reported.

2.2.4 Imaging data acquisition and analysis

Imaging data acquisition was conducted with a research-dedicated 3.0 T Tim Trio scanner (Siemens, Erlangen, Germany). Stimuli were projected onto a screen to be viewed with a rear-view mirror, and participant responses were recorded with an MR-compatible response box held in the right hand. Scanner noise was minimized with earplugs, and head motion was minimized with foam pads. Functional T2*-weighted images were collected using EPI sequences (TR = 1500 ms, TE = 30 ms, FA = 90^{o}, FOV = 192 x 192 mm, matrix size = 64 x 64 pixels, 28 oblique axial slices, slice thickness = 4 mm, gap = 0.4 mm, voxel size = 3 x 3 x 4 mm). For each functional scan, eight discarded volumes were collected prior to the start of the task. Coplanar T1-weighted structural

images were acquired for registration of functional data. For further registration, visualization, and normalization to standard atlas space, high-resolution structural images were acquired using T1-weighted 3D multi-echo magnetization-prepared rapid-acquisition gradient echo (MEMPRAGE) sequences (TR = 2530 ms; TI = 1200 ms; FA = 7°, FOV = 256 x 256 mm; matrix size = 256 x 256 mm, 192 oblique axial slices, voxel size = 1 x 1 x 1 mm).

After the data were visually inspected for head motion and data quality, all analyses were conducted using the FSL (Functional MRI of the Brain Software Library, www.fmrib.ox.ac.uk/fsl) software FEAT (fMRI Expert Analysis Tool). Standard preprocessing steps were completed including motion correction, spatial normalization, global intensity normalization, high-pass filtering, and 4-mm spatial smoothing (Smith et al., 2004).

First level (within-run analyses) were then completed using a general linear model approach. The model included each of seven regressors for anticipation periods for each type of trial (neutral control $0, gain 0$, gain 1$, gain $5, lose 0$, lose 1$, lose $5) and one regressor for outcome periods. The anticipation period was modeled by a unit amplitude response of 1 s duration starting with the disappearance of the trial indicator that was subsequently convolved with a canonical hemodynamic response function, and the outcome period was modeled by a unit amplitude response of 1 s duration starting with the appearance of feedback, again convolved with a canonical hemodynamic

response function. Pairwise contributions of beta parameter estimates for these conditions were compared and represented in contrast images. Gain $5 trials were contrasted against Gain $0 trials and Lose $5 vs Lose$0 trials to evaluate anticipation of gain and the anticipation of avoiding loss. Data were combined across runs (within-subject) using a fixed-effects model then across subjects using a mixed-effects model via FSL's Local Analysis of Mixed Effects (FLAME) tool (Beckmann et al., 2003), with age, gender, education, handedness, ethnicity, and number of response omissions as covariates. Resulting group maps were cluster corrected to control for multiple comparisons using Analysis of Functional NeuroImages (AFNI)'s Alpha Sim Monte Carlo simulations (R.W. Cox, National Institute of Health, Bethesda, Maryland) at a z-threshold of 2.58 and a probability of spatial extent at a p-value of < 0.05. Additional analyses for *a priori* regions of interest were conducted in VTA and nucleus accumbens. The nucleus accumbens mask was drawn from the Harvard-Oxford subcortical atlas, and the VTA mask was drawn from the probabilistic VTA atlas created in our laboratory(Shermohammed et al., 2012), as no standard mask exists.

To investigate regional correlations with clinical symptoms, we interrogated the peak voxel of the activated cluster within each region from between-group contrasts. Where no group difference existed, peak voxels were identified in the at-risk group map of activation in the relevant condition.

2.2.5 Correlation Analyses

We assessed for relationships between activation in our two *a priori* regions of interest (VTA and striatum) in each of 2 contrasts (gain $5 vs gain $0 and lose $5 vs lose $0) with eight non-independent measures of clinical severity (GAF, PANSS positive, negative, and general subscales and total scores, and Comprehensive Assessment of At-Risk Mental States (CAARMS) severity, frequency, and combined scores) with exploratory correlation analyses.

2.3 Results

2.3.1 Behavioral Performance

Both the at-risk and control groups showed faster responses for trials associated with higher amounts to win (main effect of trial type [$F(1.6, 153) = 99.4$, $p < .0001$]) or avoid losing (main effect of trial type [$F(1.5,142) = 79.6$, $p < .0001$]). There was a trend toward a main effect of group for gain trials ($F(1,95) = 3.7$, $p = .06$) and avoid losing trials ($F(1,95) = 3.0$, $p = .09$) and there were no group by trial type interactions (gain trials: [$F(1.6,153) = .3$, $p = .675$]; avoid losing trials: [$F(1.5,142) = .4$, $p = 0.594$]). Response time data is summarized in Figure 3.

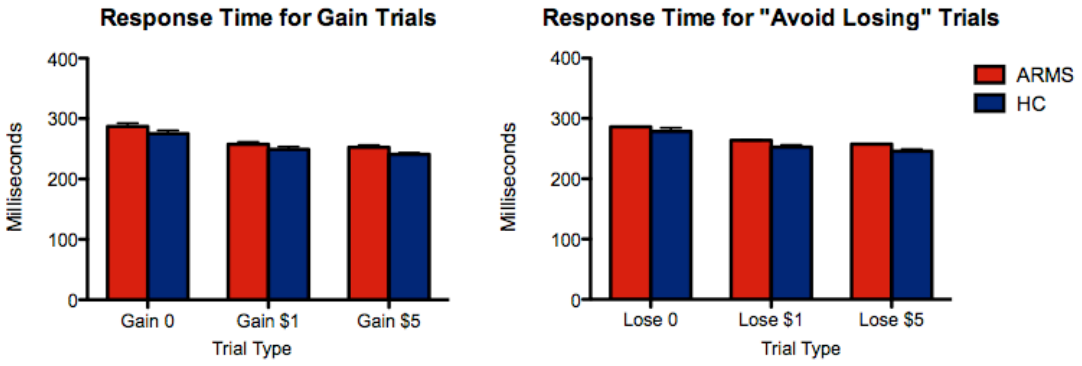

Figure 3: Response times during the monetary incentive delay task.
Main effect of trial type with no group differences. Error bars show standard error.
Error bars show standard errors.

2.3.2 fMRI Results

2.3.2.1 Activations associated with reward-anticipation

Both groups showed widely distributed activations with peaks in the striatum, midbrain, thalamus, prefrontal cortex, and visual cortex in the gain $5 > gain $0 contrast, representing activation during reward anticipation. Main effects of group were seen in the DLPFC during the anticipation of reward, with at-risk participants showing less DLPFC activation than control participants (Figure 4). In addition, mean VTA ROI activation was decreased in at-risk subjects compared to controls (p=0.03) during reward anticipation (Figure5).

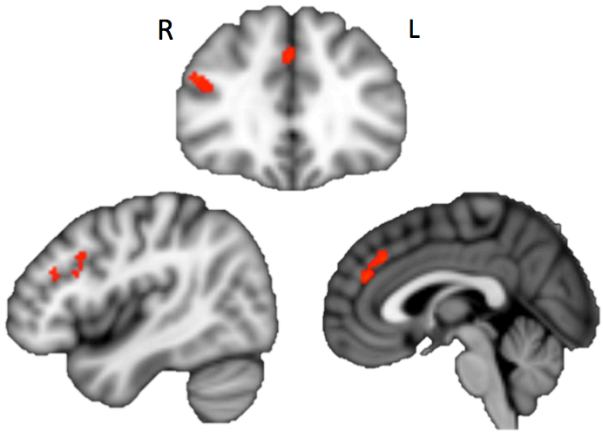

Figure 4. DLPFC hypoactivation in the at-risk group during anticipation of reward.

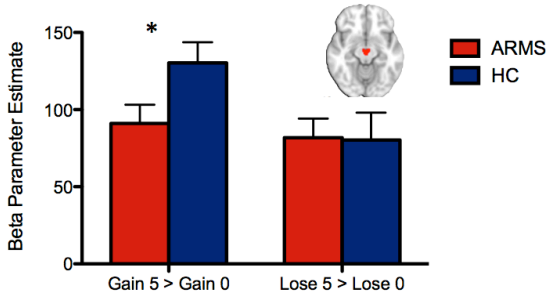

Figure 5. VTA ROI hypoactivation in the at-risk group during anticipation of reward.

2.3.2.2 Activations associated with anticipation of loss-avoidance

As in the gain $5 > gain $0 contrast, both groups showed widely distributed activations with peaks in the striatum, midbrain, thalamus, prefrontal cortex, and visual

cortex in the lose $5 vs lose $0 contrast representing the anticipation of loss avoidance. Main effects of group were seen in the medial prefrontal cortex (mPFC), with at-risk participants showing less mPFC activation than control participants (Figure 6).

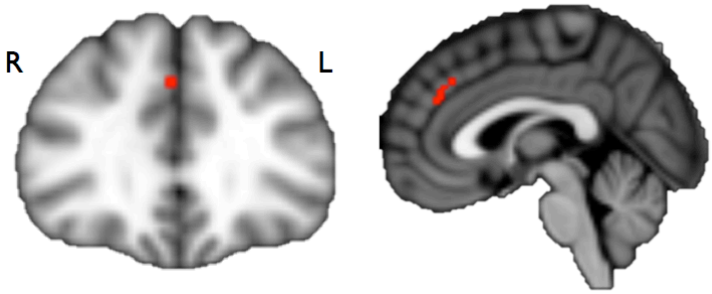

Figure 6. MPFC hypoactivation in the at-risk group during the anticipation of loss-avoidance.

2.3.2.3 Correlations between activations and clinical measures

Exploratory analyses related eight non-independent measures of clinical severity (CAARMS frequency, severity and combined scores, PANSS and its subscales, and GAF) to activation in the VTA, NAcc, DLPFC and mPFC during reward-anticipation and the anticipation of loss avoidance. Activation during the anticipation of loss avoidance was inversely correlated (non-corrected) with symptom severity (r=-0.26, p=0.04) as indexed by combined CAARMS frequency and severity scores, with decreasing Nacc activation associated with increasing symptom severity.

2.4 Discussion

In this fMRI study of anticipation of reward and loss-avoidance, behavior and fMRI activations of at-risk individuals and healthy control subjects were compared.

Faster responses for incentivized trials for all participants with no group differences or interactions were demonstrated, suggesting that both groups understood the difference between incentivized and unincentivized trials. At risk individuals showed decreased DLPFC and VTA activation during reward anticipation and decreased medial prefrontal activation during both the anticipation of reward and the anticipation of loss avoidance. NAcc activation during the anticipation of loss avoidance was inversely correlated with symptom severity, with less Nacc activation predicting increased symptom severity.

Together, these findings suggest that at-risk individuals, like individuals with established schizophrenia(Juckel et al., 2006), fail to adequately recruit the dopaminergic reward system in response to reward-predicting stimuli and that decreased recruitment is associated with increased symptom severity. They are consistent with predictions of the aberrant salience hypothesis for how dopaminergic dysfunction could lead to the clinical symptoms, with dysregulation leading to increased noise in the system that can prevent dopaminergic signals linked to stimuli indicating reward from being detected (Roiser 2008). In other words, the increased noise in the system could "drown out" motivational signals, which could lead to negative symptoms like avolition and decreases in psychosocial function caused by lack of interest and social withdrawal(Howes and Kapur, 2009) while the misattribution of salience to unimportant items internal and external stimuli may then, when experienced by

individuals with different sets of cognitive and social experiences, lead to an array of different delusions and hallucinations (Kapur, 2003).

While fMRI-measured deficits in reward-processing in support of the dopamine-dependent aberrant salience model are common in established schizophrenia(Juckel et al., 2006; Corlett et al., 2007; Nielsen et al., 2012), findings of such deficits in the at-risk mental state can provide evidence that these abnormalities are present prior to the development of the disease. Findings from the current study provide such evidence in concert with a previous PET study showing striatal dopaminergic overactivity (increased striatal [18F]-dopa uptake) in individuals with prodromal symptoms(Howes et al., 2009), and a previous fMRI study in the at-risk mental state, which showed decreased NAcc activation at trend level during the anticipation of loss avoidance (Juckel et al., 2012).

Not only did at-risk individuals show decreased VTA activation during reward anticipation in this study, they also showed decreased DLPFC activation. This is consistent with findings in healthy controls performing a similar task that showed that DLPFC activation drives VTA activation to reward-related stimuli(Ballard et al., 2011). It is also consistent with the large body of literature highlighting hypofrontality in schizophrenia and with the growing body of literature showing prefrontal cortical activation alterations as one of the most robust and replicable findings in the at-risk

mental state across paradigms(Broome et al., 2010a; 2010b; Fusar-Poli et al., 2010b; 2011; Fusar-Poli, 2012; Yaakub et al., 2013).

One limitation of this study is that it is not yet known which participants will develop psychosis in the long term. Transition to psychotic disorder is a commonly used outcome measure for studies in at-risk individuals; however, this binarization of outcomes is artificial, and the correlation with symptom severity seen in this study could serve as an appropriate proxy. During a two-year follow-up, only six participants in this sample have converted to psychosis. It is not uncommon for recent studies of at-risk subjects to report lower-than-population conversion rates (Yung et al., 2008; Fusar-Poli et al., 2012), partly because study participation can itself be therapeutic, and partly because of lead-time bias (Nelson et al., 2013), with earlier detection of at-risk status leading to longer periods between identification and transition. For this reason, a consensus beginning to emerge is that such predictive analyses could continue to be beyond the reach of even large studies like this one. Thus, while this study cannot identify reliable predictors of psychosis during 'treatment as usual', it provides a large data set for characterizing those at risk. Perhaps more pertinently, it may be that correlations with current symptoms and functioning are the best proxies for those predictors likely to be obtained. Separate from the goal of predicting conversion, studying an at-risk population also offers the opportunity characterize illness-associated dysfunction, while avoiding common illness-associated confounds, like long-term

neuroleptic treatment.

One strength of this sample is its size: this is one of the largest functional imaging studies comparing individuals at risk for psychosis and control participants(Fusar-Poli, 2012), as part of the Longitudinal Youth At Risk Study (LYRIKS) led by Singapore's National Institute of Mental Health. Singapore's structured society, small geographical area, and comprehensive health, military, and educational systems offer multiple advantages for a longitudinal study. Low rates of nicotine, alcohol, and other comorbid substance abuse in Singapore(Verma et al., 2002; Picco et al., 2012; Subramaniam et al., 2012) are other unique advantages.

An additional notable study feature is that it is part of a theoretically-grounded fMRI battery of four tasks targeting stress reactivity, reward anticipation, working memory(Yaakub et al., 2013) and hippocampus-dependent learning. This battery targets memory and motivational systems as potential primary mechanisms in the onset of schizophrenia. It is nested within a larger neurocognitive battery that includes standard tests and novel assessments of memory-based predictive perception(Keefe and Kraus, 2009; Keefe et al., 2011). This coherent approach allows tracking of participants across the functional battery and integration of imaging findings with neurocognitive data from a larger sample.

In conclusion, findings from this study demonstrate abnormalities in reward-system function as measured by fMRI in individuals prone to psychosis prior to

development of established disease. Decreased engagement of the prefrontal cortex and dopaminergic midbrain in response to reward-related stimuli are thus potential biomarkers for the development of schizophrenia, suggesting reward-system dysfunction may represent biological vulnerability to this debilitating illness.

3. Decreased dopaminergic midbrain engagement during hippocampus-dependent learning in individuals at risk for psychosis

3.1 Introduction

Schizophrenia is associated with hippocampal pathology(Heckers and Konradi, 2010), with hippocampal volume reduction(Adriano et al., 2012) being one of the most prominent findings in the disease. This dysfunction is accompanied by impaired performance on hippocampus-dependent memory tasks involving relational memory but with relatively spared item memory(Achim and Lepage, 2003). Individuals with schizophrenia also show reductions in task-associated activations in multiple hippocampus-dependent memory tasks, including episodic encoding(Jessen et al., 2003), relational memory formation(Ongür et al., 2006), word and face recognition(Rametti et al., 2009), novelty recognition(Weiss et al., 2004), and virtual navigation(Ledoux et al., 2013). The decreased activation for stimuli of interest seen in these studies was likely secondary to increased engagement at baseline for all stimuli, as suggested by two separate studies showing the hippocampus does not habituate to repeated face presentations in schizophrenia(Holt et al., 2006; Williams et al., 2013), with lack of discriminability in hippocampal activation for old and new stimuli correlated with decreased memory performance, suggesting the decreased ability of the hippocampus to habituate might contribute to the memory deficits in the disorder(Williams et al., 2013).

Aside from hippocampal dysfunction, the other most prominent finding in schizophrenia is dopaminergic dysfunction(Howes and Kapur, 2009), with many arguing that prefrontal hypodopaminergia and striatal hyperdopaminergia provide the pathophysiologic basis of the disease. Dopaminergic and hippocampal function have major effects each other in healthy individuals(Lisman and Grace, 2005; Shohamy and Adcock, 2010) and their dysfunctions are highly interrelated in schizophrenia(Grace, 2012), offers a potential unifying mechanism for the progressive dopaminergic and hippocampal pathology so prominent in the development of disease. Consistent with this hypothesis, both hippocampal(Allen et al., 2011) and dopaminergic(Howes et al., 2009) dysfunction begin to emerge prior to the onset of the illness in a putatively prodromal period termed the at-risk mental state for psychosis(Yung et al., 2005). Thus, neurocognitive functional imaging of the hippocampus and dopaminergic midbrain offers candidate indices of vulnerability and of impending disease progression.

In a previous fMRI study in healthy participants, imaging of the hippocampus and dopaminergic midbrain was conducted while participants performed the acquired equivalence task(Shohamy and Wagner, 2008). Hippocampal and midbrain activations during learning correlated with later generalization of learned associations, suggesting that a cooperative hippocampal midbrain interaction may support generalization. This task was adapted for use in the current study, as it provides the opportunity to show

abnormalities in activations of these two key regions during learning of associations in individuals at-risk for developing schizophrenia.

In the current study, we compared fMRI activation associated with learning associations between faces and scenes in healthy control participants and a large, well-characterized cohort of at-risk individuals. We characterized individuals at risk for the development of schizophrenia relative to healthy individuals with respect to behavior, function of the hippocampus as modulated by the midbrain, and correlations between imaging measures and behavioral performance. Additionally, we examined the relationship between imaging measures and clinical status. We predicted that individuals at-risk for schizophrenia would exhibit decreased engagement of the dopaminergic midbrain associated with deficits in relational memory and increased clinical severity.

3.2 Methods

3.2.1 Participants

Sixty-nine at-risk and 40 healthy control volunteers between 14 and 29 years of age participated. Help-seeking participants were recruited from the Longitudinal Youth At-Risk Study (LYRIKS) through Singapore Institute of Mental Health clinics, armed forces, and community mental health services. The at-risk group was identified using the Comprehensive Assessment of At-Risk Mental States(Yung et al., 2005) (CAARMS). Healthy control participants were recruited through public advertisements in print,

social and online media and were matched for age with at-risk participants. Participants were excluded for current substance abuse or a history of serious medical or neuropsychiatric disorders, including mental retardation. Five at-risk participants and five controls were excluded for excessive head motion (rotation > 2 degrees, absolute displacement > 3 mm, or relative displacement > 1 mm). One at-risk participants and one control were excluded for technical issues with behavioral data recording. One at-risk participant was excluded due to an incidental brain finding. In total, data from 62 at-risk and 34 control participants were included. Thirty-five of the included at-risk participants were taking antidepressant medications (selective serotonin reuptake inhibitors [n=28]; tricyclic or tetracyclic antidepressants [n=4]; combination of antidepressant subtypes [n=3]). Two of the at-risk participants on antidepressants were also on low dose antipsychotics (one on quetiapine, one on chlorpromazine). Both at-risk and control participants completed a battery of neurocognitive tests assessing a range of functions, including working memory, attention, vigilance, and a standard IQ proxy, the Wechsler Abbreviated Scale of Intelligence Vocabulary Subtest (The Psychological Corporation, 1999). At-risk participants were assessed using the Positive and Negative Syndrome Scale (PANSS)(Kay, 1990), Brief Assessment of Cognition in Schizophrenia(Keefe et al., 2004), and Global Assessment of Functioning (GAF) scale (DSM-IV-TR, p. 34). Because left-handedness is more common in schizophrenia, we did not attempt to balance the

groups, to avoid introducing bias; however, analyses included handedness (assessed using an inventory(Annett, 1967)) as a covariate.

Permission to enroll participants was obtained from the Singapore National Healthcare Group Domain Specific Review Board. Participants over 21 gave written informed consent after a full study description. Participants under 21 gave assent to written consent obtained from their parent or guardian.

3.2.2 Stimuli

The stimulus set was composed of images of 16 neutral faces and 16 neutral outdoor scenes. The faces and scenes were divided into 8 sets. Each set included two faces (F1, F2) to be paired with two scenes (S1, S2). This resulted in four associations for each set: F1–S1, F1–S2, F2–S1, F2–S2, for a total of 32 associations.

3.2.3 Task

During the learning phase of the task, participants were trained on face-scene associations (Figure 7). During each training trial, participants determine which scene is associated with a face by choosing which of two presented scene choices go with that face and receiving feedback on their response (stimulus and choice displayed for 3 seconds, feedback displayed for 1 second). Each face-scene association is learned individually, but there is partial overlap: pairs of faces are associated with a common scene (F1-S1, F2-S1). To prevent simple stimulus-response learning strategies, a scene that is the correct choice for one face is the incorrect choice for a different face.

Participants also see a second association for one of the faces (F1-S2) intermixed with the other associations. The additional learning of the F1-S2 association is expected to lead to the association of F2 and S2 (Shohamy and Wagner, 2008). Each of the face-scene associations is repeated 12 times during learning. A test phase follows immediately after the second learning phase. Trained and untrained (generalized) associations are tested six times during test. Trained and untrained associations are intermixed pseudorandomly with the constraint that no associations appear consecutively. Images are presented for 3 seconds during this phase and feedback is not presented so that no new learning can occur.

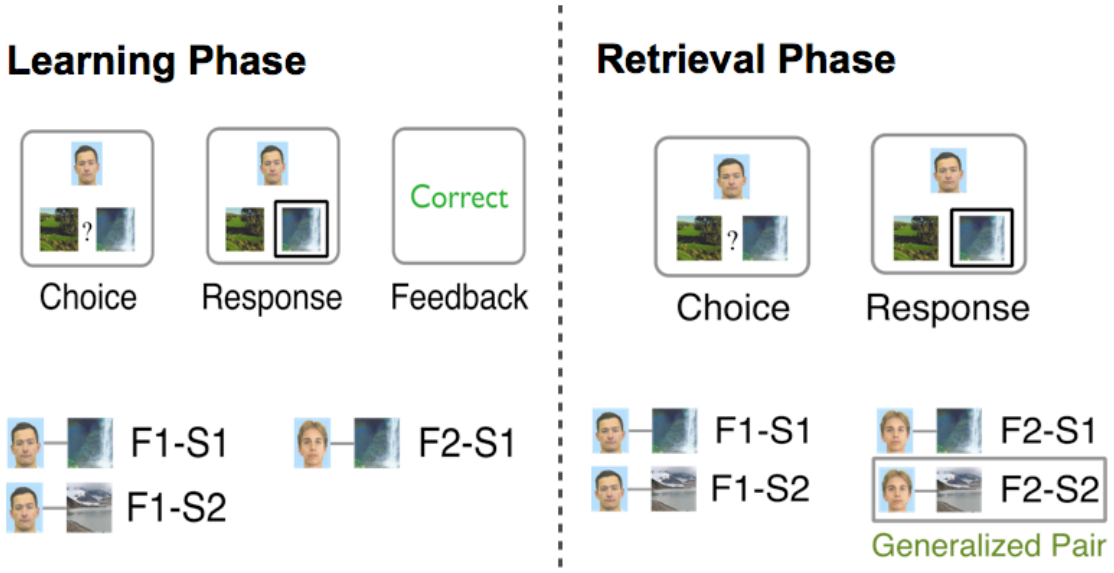

Figure 7. Acquired equivalence task design.
Feedback is used to learn a series of overlapping associations. During a later probe phase, participants' ability to generalize this knowledge to new associations is tested.

An emotional face processing task(Hall et al., 2008), reward anticipation task (Knutson et al., 2001), and working memory paradigm (Chee and Choo, 2004) were administered after this task. We have previously reported findings from the working memory (Yaakub et al., 2013) and emotional face processing paradigms; findings from the reward anticipation task will be reported in a subsequent manuscript.

3.2.4 Behavioral data analysis

Accuracy and response times during testing were collected to assess. Group differences in these measures during the test phase were assessed with 2 condition (trained versus generalized; within-subjects) x 2 group (at-risk versus control; between subjects) repeated measures analyses of variance (ANOVAs). When the sphericity assumption was violated, Greenhouse-Geisser corrected values were reported. Post-hoc t-tests were conducted when significant effects were demonstrated by the ANOVAs. Results with p-values < 0.05 were considered significant.

3.2.5 Imaging data acquisition and analysis

Imaging data acquisition was conducted with a research-dedicated 3.0 T Tim Trio scanner (Siemens, Erlangen, Germany). Stimuli were projected onto a screen to be viewed with a rear-view mirror, and participant responses were recorded with an MR-compatible response box held in the right hand. Scanner noise was minimized with earplugs, and head motion was minimized with foam pads. Functional T2*-weighted images were collected using EPI sequences (TR = 1500 ms, TE = 30 ms, FA = 90^{o}, FOV =

192 x 192 mm, matrix size = 64 x 64 pixels, 28 oblique axial slices, slice thickness = 4 mm, gap = 0.4 mm, voxel size = 3 x 3 x 4 mm). For each functional scan, eight discarded volumes were collected prior to the start of the task. Coplanar T1-weighted structural images were acquired for registration of functional data. For further registration, visualization, and normalization to standard atlas space, high-resolution structural images were acquired using T1-weighted 3D multi-echo magnetization-prepared rapid-acquisition gradient echo (MEMPRAGE) sequences (TR = 2530 ms; TI = 1200 ms; FA = 7°, FOV = 256 x 256 mm; matrix size = 256 x 256 mm, 192 oblique axial slices, voxel size = 1 x 1 x 1 mm).

After the data were visually inspected for head motion and data quality, all analyses were conducted using the FSL (Functional MRI of the Brain Software Library, www.fmrib.ox.ac.uk/fsl) software FEAT (fMRI Expert Analysis Tool). Standard preprocessing steps were completed including motion correction, spatial normalization, global intensity normalization, high-pass filtering, and 4-mm spatial smoothing (Smith et al., 2004).

First level (within-run analyses) were then completed using a general linear model approach. Each trial was modeled as an event using a canonical hemodynamic response function. Each trial type (F1-S1, F1-S2, F2-S1) as well as correct and incorrect trials was modeled separately. Pairwise contributions of beta parameter estimates for these conditions were compared and represented in contrast images. Data will be

combined across runs, for each subject, using a fixed-effects model, and combined across subjects using a mixed-effects model via FSL's FLAME tool (Beckmann et al., 2003), with age, gender, education, handedness, ethnicity, and number of response omissions as covariates. Resulting group maps were cluster corrected to control for multiple comparisons using Analysis of Functional NeuroImages (AFNI)'s Alpha Sim Monte Carlo simulations (R.W. Cox, National Institute of Health, Bethesda, Maryland) at a z-threshold of 2.58 and a probability of spatial extent at a p-value of < 0.05. Additional analyses for *a priori* regions of interest were conducted in VTA and bilateral hippocampi. The hippocampal masks were drawn from the Harvard-Oxford subcortical atlas, and the VTA mask was drawn from the probabilistic VTA atlas created in our laboratory(Shermohammed et al., 2012), as no standard mask exists.

To investigate regional correlations with clinical symptoms, we interrogated the peak voxel of the activated cluster within each region from between-group contrasts. Where no group difference existed, peak voxels were identified in the at-risk group map of activation in the relevant condition.

3.2.6 Correlation Analyses

We assessed for relationships between activation in the VTA, hippocampus, and DLPFC during associative learning with eight non-independent measures of clinical severity (GAF, PANSS positive, negative, and general subscales and total scores, and

CAARMS severity, frequency, and combined scores) with exploratory correlation analyses.

3.3 Results

3.3.1 Behavioral Performance

Both at-risk and controlled participants performed well on trained associations (at-risk: mean 90%, SD 8%, control: mean 93%, SD 5%) with decreased performance on associations requiring generalization (at risk: mean 81%, SD 12%, control: mean 85%, SD 13%), resulting in a main effect of trial type ["generalized" vs. "trained"; $F(1,94) = 46.32$, $p < .000001$]. Deficits in relational memory in at-risk participants was also revealed with a main effect of group on memory performance [$F(1,94) = 4.61$, $p = .03$]. There was no group × trial type interaction [$F(1,94) = .023$, $p > .5$]. Memory performance is summarized in Figure 8.

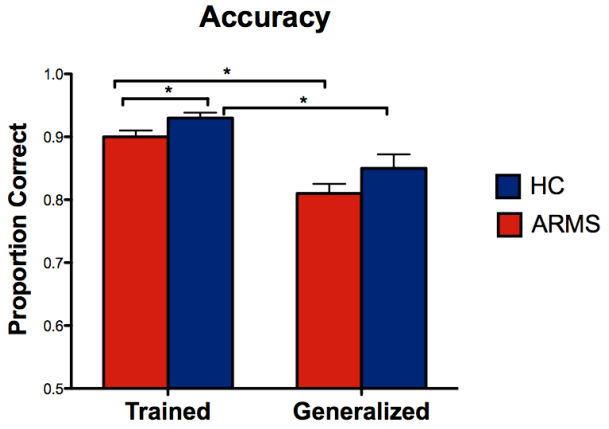

Figure 8: Memory performance at test on trained and generalized associations. *Significant difference ($p<0.05$). Error bars show standard errors.

3.3.2 fMRI Results

3.3.2.1 Activations during learning of associations

FMRI data collected during all correct association-learning trials was contrasted against baseline activation. This revealed robust hippocampal activation in both groups in addition to activation in the VTA, striatum, and DLPFC. Main effects of group were seen in the DLPFC, with increased DLPFC activation seen in the at-risk group compared to controls (Figure 9A). The at-risk group showed decreased VTA activation at the ROI level (Figure 9B).

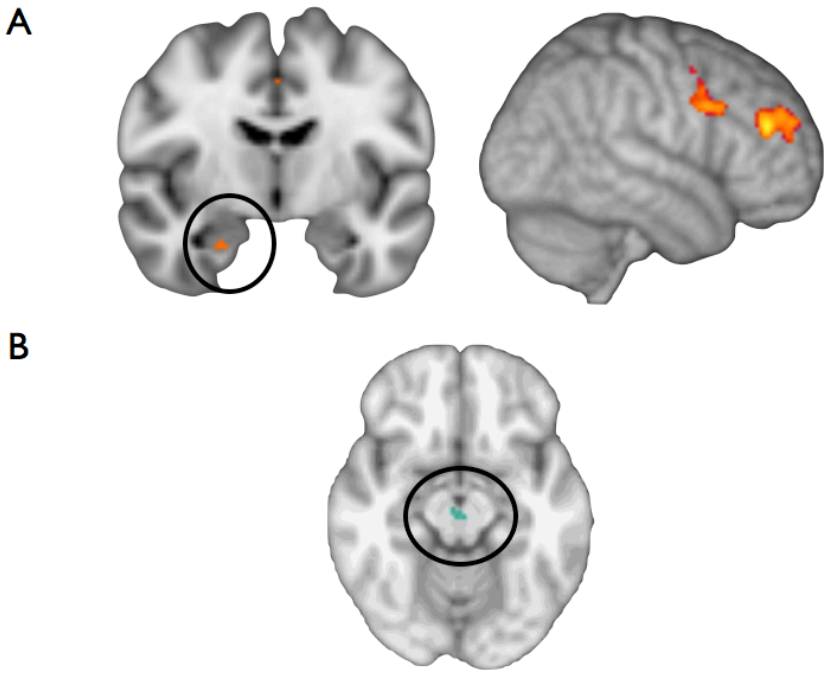

Figure 9. (A) DLPFC and hippocampal hyperactivations in the at-risk group. (B) VTA hypoactivation in the at-risk group.

3.3.2.2 Correlations with behavior and clinical symptoms

VTA activation was inversely correlated with generalization performance in UHR individuals (r=-0.3, p=0.01). Both VTA (r=-0.3, p=0.008) and hippocampal (r=-0.3, p=0.04) activations were negatively correlated with clinical severity as measured by positive and negative syndrome scale (PANSS) scores. VTA activation was positively correlated with social functioning as assessed with the High Risk Social Challenge (HiSoc) task (r = 0.4, p = .01). See Figure 10. Generalization performance was also highly correlated with performance on this measure of social functioning (r = 0.5, p = .0003).

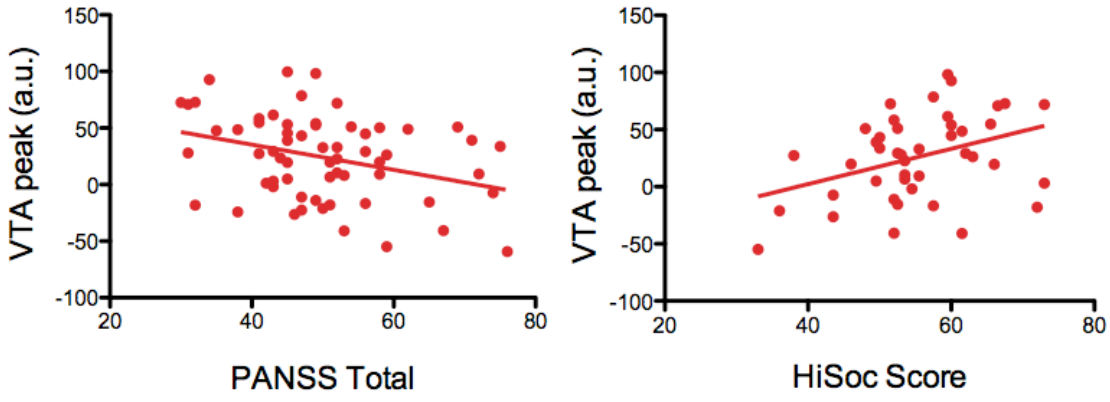

Figure 10. VTA activation in the at-risk group decreases with increasing clinical severity and increases with increasing social functioning.

3.4 Discussion

In this fMRI study of hippocampus-dependent learning, behavior and fMRI activations of at-risk individuals and healthy control subjects while performing this task were compared. Relational memory deficits were demonstrated in the at-risk individuals**.** Increased DLPFC and hippocampal activation during learning were

demonstrated in addition to decreased VTA activation. The decreased VTA activation during learning was correlated with greater clinical severity and decreased performance on a measure of social function. Social function was also predicted by ability to generalize information to new associations.

Together, these findings suggest that at-risk individuals have limited VTA recruitment that during learning that predicts symptom severity despite potential compensatory hyperactivations in the DLPFC and hippocampus. The dysfunctional activation of these key regions connecting the dopaminergic and glutamatergic models of schizophrenia during relational learning highlights the major role that deficiencies in learning play in the disability associated with the disease. Deficiencies in cognition, including relational memory, and social dysfunction are two of the primary disabling deficits in schizophrenia(Mueser and McGurk, 2004). This study shows relationships between these deficiencies in the at-risk mental state. It makes an even more interesting discovery that altered activation in prominent regions associated with schizophrenia pathophysiology during a relational memory task also predict social dysfunction, offering an avenue into future studies pathophysiological basis of social dysfunction in both schizophrenia and its prodrome.

Dopaminergic system dysfunction and hippocampal dysfunction are prominent in established schizophrenia and are receiving interest in the at-risk mental state. Findings from the current study showing altered hippocampal and VTA activity in the

at-risk mental state during learning highlight how early in the course of the illness these abnormalities are detectable. This is in line with previous neuroimaging studies implicating dopaminergic dysfunction(Howes et al., 2009) in the at-risk mental state in addition to medial temporal lobe dysfunction(Allen et al., 2011) during an episodic memory task in the at-risk mental state. Another fMRI-PET study of at-risk individuals went even further to show that the at-risk mental state was associated with an altered relationship between MTL activation and striatal dopamine function(Allen et al., 2012), consistent with Lisman and Grace's model that striatal hyperdopaminergia is driven by MTL dysfunction(Lisman et al., 2008).

In addition to hippocampal and VTA activation alterations in the at-risk mental state, this study also demonstrates alterations in DLPFC activation. Altered DLPFC function in this study that targets building relationships between items in memory integrates and extends two associated findings from previous literature. First, the DLPFC is activated during the processing of relationships between items in memory (Blumenfeld and Ranganath, 2007). In addition, individuals with schizophrenia have prominent dysfunction in relational memory(Ongür et al., 2006). Abnormalities in this key region associated with both reward(Ballard et al., 2011) and memory(Blumenfeld et al., 2011) are demonstrated in this associative learning task that engages both systems in the at-risk mental state. This highlights the importance of the interplay between prefrontal cortex, hippocampus, and VTA in the associative learning that occurs daily to

shape individuals' view of the world. When this learning is dysfunctional, as in the at-risk mental state, it may result in misshapen representations. The neurofunctional abnormalities demonstrated in this study provide a neural basis for the dysfunctional learning that is likely occuring.

While this study makes a substantial contribution to characterizing hippocampus-dependent learning in the at-risk mental state, it has several limitations. First, it is not yet known which participants will develop psychosis in the long term. Transition to psychotic disorder is a commonly used outcome measure for studies in at-risk individuals; however, this binarization of outcomes is artificial, and there has been increasing interest in functional outcome as an at least equally important outcome measure. During a two-year follow-up, only six participants in this sample have converted to psychosis. It is not uncommon for recent studies of at-risk subjects to report lower-than-population conversion rates (Yung et al., 2008; Fusar-Poli et al., 2012), partly because study participation can itself be therapeutic, and partly because of lead-time bias (Nelson et al., 2013), with earlier detection of at-risk status leading to longer periods between identification and transition. For this reason, a consensus beginning to emerge is that such predictive analyses could continue to be beyond the reach of even large studies like this one. Thus, while this study cannot identify reliable predictors of psychosis during 'treatment as usual', it provides a large data set for characterizing those at risk. Perhaps more pertinently, it may be that correlations with current symptoms and

functioning are the best proxies for those predictors likely to be obtained. Separate from the goal of predicting conversion, studying an at-risk population also offers the opportunity characterize illness-associated dysfunction, while avoiding common illness-associated confounds, like long-term neuroleptic treatment.

This study also has several strengths. One strength of the study sample itself is its size: this is one of the largest functional imaging studies comparing individuals at risk for psychosis and control participants(Fusar-Poli, 2012), as part of the Longitudinal Youth At Risk Study (LYRIKS) led by Singapore's National Institute of Mental Health. Singapore's structured society, small geographical area, and comprehensive health, military, and educational systems offer multiple advantages for a longitudinal study. Low rates of nicotine, alcohol, and other comorbid substance abuse in Singapore(Verma et al., 2002; Picco et al., 2012; Subramaniam et al., 2012) are other unique advantages.

In summary, this study of hippocampal learning in individuals at-risk for the development of schizophrenia demonstrates alterations in brain regions commonly associated with reward and learning, including the VTA, hippocampus, and DLPFC. Decreased VTA activation was associated with both symptom severity and social functioning, suggesting that dysfunction in this key region in the at-risk mental state may impart vulnerability for the progression to disease and the global deficits that generally accompany it.

4. Increased fear network engagement during viewing of neutral faces in individuals at risk for psychosis

4.1 Introduction

Diathesis-stress models of psychosis posit that psychosocial stress may cause triggering or worsening of symptoms of psychosis in vulnerable individuals(Corcoran et al., 2003; van Winkel et al., 2008; Aiello et al., 2012). Patients with psychosis exhibit increased emotional reactivity to daily life stressors(Myin-Germeys et al., 2001) and increased psychotic symptoms in response to stressors(Norman and Malla, 1994). Symptomatic and emotional reactivity to stressors are also evident prior to disease onset in individuals at risk for developing psychosis(Palmier-Claus et al., 2012), and correlate with subclinical psychotic experience(Lataster et al., 2009). Stress hyper-reactivity may thus reflect decreased resilience and predict poor functional outcome and risk for onset of psychosis.

In line with their increased emotional reactivity to everyday stressors, individuals with schizophrenia display increased emotional reactivity to neutral stimuli(Williams et al., 2004; Haralanova et al., 2011), along with increases in blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) contrast (hereafter, 'activation') in emotion-related regions such as the amygdala, ACC, medial mPFC, and parahippocampal cortex (PHC)(Surguladze et al., 2006; Hall et al., 2008; Lakis and Mendrek, 2013). In this study, we sought to determine whether individuals at risk for psychosis show similar evidence of emotional hyper-reactivity using an

emotional face-processing paradigm. Human faces are biologically relevant stimuli, and deficits in the processing of emotion in human faces are prominent in established psychosis(Morris et al., 2009) and are linked with impairments in communication and occupational function(Hooker and Park, 2002), social cognition(Pinkham and Penn, 2006), and social skill(Pinkham et al., 2007). Identifying altered patterns of brain activation in response to human faces in at-risk individuals may help elucidate underlying mechanisms of functional impairments in social and role functioning that exist prior to psychosis (Carrión et al., 2011). Such functional impairments, measured by both Global Functioning (Social and Role scales)(Cornblatt et al., 2007) and the widely clinically used Global Assessment of Functioning (GAF) scale (DSM-IV-TR, p. 34), predict not only transition to psychosis(Fusar-Poli et al., 2010a; Nelson et al., 2013) but also, perhaps even more importantly, long-term functional outcome(Carrión, 2013).

Although multiple large behavioral studies have documented facial emotion discrimination deficits in clinically at-risk individuals(Phillips and Seidman, 2008; van Rijn et al., 2010; Addington et al., 2012; Amminger et al., 2012), the two extant fMRI studies (Seiferth et al., 2008; Gee et al., 2012) studied twenty or fewer at-risk individuals. Moreover, neither of the extant studies included an explicit baseline that would permit assessment of responses to neutral faces. Understanding responses to neutral faces is important because of its potential mechanistic relevance to symptoms like paranoia and because fear-network hyper-reactivity to neutral faces has been demonstrated in

schizophrenia(Hall et al., 2008). In the current study we followed Hall et al. (Hall et al., 2008) in asking participants to discriminate genders rather than emotions, because discriminating emotions has been shown to decrease limbic system activation(Hariri et al., 2000). We added a baseline condition to permit explicit contrasts of fMRI responses to both fearful and neutral face stimuli.

In this study, we compared fMRI activation associated with viewing fearful and neutral face stimuli in healthy control participants and a large, well-characterized cohort of at-risk individuals with minimal substance use. We examined *a priori* regions of interest (ROIs) implicated in emotion and threat detection. These included regions with documented hyper-reactivity to neutral faces in schizophrenia (amygdala, mPFC, ACC, PHC, and fusiform gyrus; (Holt et al., 2006; Surguladze et al., 2006; Hall et al., 2008; Habel et al., 2010), plus a region with documented hyper-reactivity during threat monitoring in trait-anxious individuals (Mobbs et al., 2010; Somerville et al., 2010), the bed nucleus of the stria terminalis/ventral basal forebrain (hereafter BNST). Hyperactivation of these ROIs, particularly to neutral face stimuli, would be consistent with hypervigilance and increased stress reactivity, thus representing potential prognostic indicators. Thus, in these fear network ROIs, we expected to find increased activation and significant positive correlations with clinical severity for at-risk individuals.

4.2 Methods

4.2.1 Participants

Sixty-nine at-risk and 40 healthy control volunteers between 14 and 29 years of age participated. Help-seeking participants were recruited from the Longitudinal Youth At-Risk Study (LYRIKS) through Singapore Institute of Mental Health clinics, armed forces, and community mental health services. The at-risk group was identified using the Comprehensive Assessment of At-Risk Mental States(Yung et al., 2005) (CAARMS). Healthy control participants were recruited through public advertisements in print, social and online media and were matched for age with at-risk participants. Participants were excluded for current substance abuse or a history of serious medical or neuropsychiatric disorders, including mental retardation. Four at-risk participants and one control were excluded for excessive head motion (rotation > 2 degrees, absolute displacement > 3 mm, or relative displacement > 1 mm). Eight at-risk participants and one control were excluded for poor performance (chance-level identification of letters presented in gray oval stimuli). One at-risk participant was excluded due to an incidental brain finding. In total, data from 56 at-risk and 38 control participants were included. Twenty-nine at-risk participants were taking antidepressant medications (selective serotonin reuptake inhibitors [n=23]; tricyclic or tetracyclic antidepressants [n=4]; combination of antidepressant subtypes [n=2]). The two participants who were

taking antipsychotic medication were among those excluded for motion; thus all participants in the analyzed dataset were antipsychotic naïve.

Both at-risk and control participants completed a battery of neurocognitive tests assessing a range of functions, including working memory, attention, vigilance, and a standard IQ proxy, the Wechsler Abbreviated Scale of Intelligence Vocabulary Subtest (The Psychological Corporation, 1999). At-risk participants were assessed using the Positive and Negative Syndrome Scale (PANSS)(Kay, 1990), Brief Assessment of Cognition in Schizophrenia(Keefe et al., 2004), and Global Assessment of Functioning (GAF) scale (DSM-IV-TR, p. 34). Because left-handedness is more common in schizophrenia, we did not attempt to balance the groups, to avoid introducing bias; however, analyses included handedness (assessed using an inventory(Annett, 1967)) as a covariate.

Permission to enroll participants was obtained from the Singapore National Healthcare Group Domain Specific Review Board. Participants over 21 gave written informed consent after a full study description. Participants under 21 gave assent to written consent obtained from their parent or guardian.

4.2.2 Stimuli

The stimulus set consisted of grayscale photographs of fearful and neutral faces(Matsumoto and Ekman, 1988) and visuomotor control stimuli. Fearful and neutral

faces were balanced regarding gender (male, female) and ethnicity (Asian, Caucasian). Control stimuli were luminance-matched gray ovals containing "M" or "F".

4.2.3 Task

In this block design fMRI paradigm, participants were shown fearful faces, neutral faces, or gray oval stimuli (Figure 11).

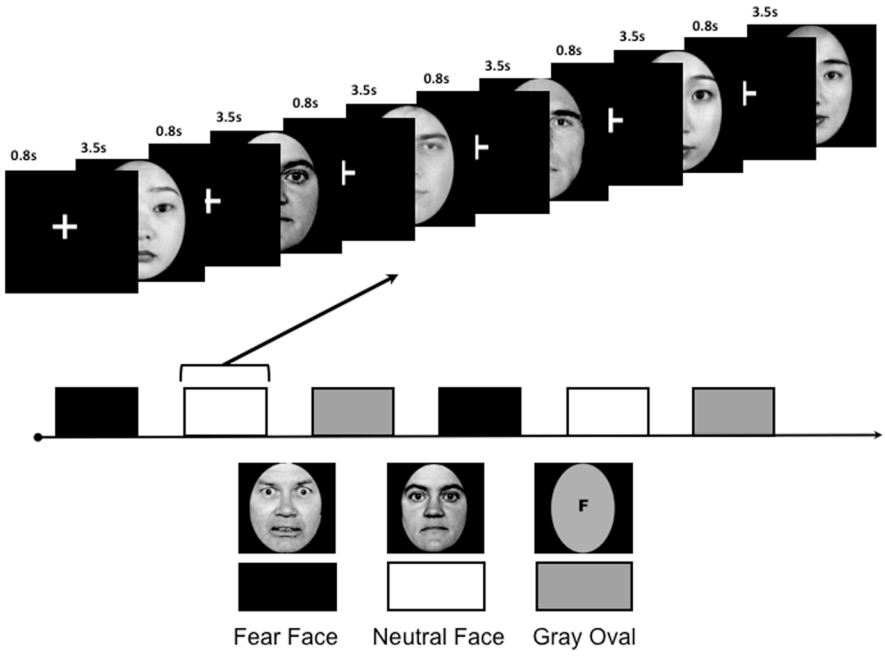

Figure 11. Emotional face processing task design.
Participants viewed blocks of fearful faces, neutral faces, and gray oval stimuli and were instructed to identify the gender of the faces or the letter presented in the gray oval stimuli ("M" or "F").

Participants were instructed to identify via button press the genders of the faces ("M" or "F") or the letters presented in gray oval stimuli ("M" or "F"). During each 26-second block, one stimulus type (fearful face, neutral face or gray oval) was presented.

Each stimulus lasted 3.5 seconds with an inter-stimulus interval (fixation cross) of 0.8 seconds. The full task was completed in one run of three blocks each, with each block consisting of six fearful faces, six neutral faces or six gray ovals. Blocks were intermingled and block order was counterbalanced across individuals.

A hippocampus-dependent learning task(Shohamy and Wagner, 2008), reward anticipation task(Knutson et al., 2001), and working memory paradigm(Chee and Choo, 2004) were administered prior to this task. We have previously reported findings from the working memory paradigm(Yaakub et al., 2013); other task findings appear in other chapters of this dissertation.

4.2.4 Behavioral data analysis

Accuracy and response times were collected for the discrimination task. Group differences in these measures were assessed with a 3 condition (gray oval versus neutral face versus fearful face; within-subjects) x 2 group (at-risk versus control; between subjects) repeated measures analysis of variance (ANOVA). When the sphericity assumption was violated, Greenhouse-Geisser corrected values were reported. Post-hoc t-tests were conducted when significant effects were demonstrated by ANOVAs. P-values less than 0.05 were considered significant.

4.2.5 Imaging data analysis

Imaging data acquisition was conducted with a research-dedicated 3.0 T Tim Trio scanner (Siemens, Erlangen, Germany). Stimuli were projected onto a screen to be

viewed with a rear-view mirror, and participant responses were recorded with an MR-compatible response box held in the right hand. Scanner noise was minimized with earplugs, and head motion was minimized with foam pads. Functional T2*-weighted images were collected using EPI sequences (TR = 1500 ms, TE = 30 ms, FA = 90^{o}, FOV = 192 x 192 mm, matrix size = 64 x 64 pixels, 28 oblique axial slices, slice thickness = 4 mm, gap = 0.4 mm, voxel size = 3 x 3 x 4 mm). For each functional scan, eight discarded volumes were collected prior to the start of the task. Coplanar T1-weighted structural images were acquired for registration of functional data. For further registration, visualization, and normalization to standard atlas space, high-resolution structural images were acquired using T1-weighted 3D multi-echo magnetization-prepared rapid-acquisition gradient echo (MEMPRAGE) sequences (TR = 2530 ms; TI = 1200 ms; FA = 7^{o}, FOV = 256 x 256 mm; matrix size = 256 x 256 mm, 192 oblique axial slices, voxel size = 1 x 1 x 1 mm).

After the data were visually inspected for head motion and data quality, all analyses were conducted using the FSL (Functional MRI of the Brain Software Library, www.fmrib.ox.ac.uk/fsl) software FEAT (fMRI Expert Analysis Tool). Standard preprocessing steps were completed including motion correction, spatial normalization, global intensity normalization, high-pass filtering, and 4-mm spatial smoothing (Smith et al., 2004).

First level (within-run analyses) were then completed using a general linear model approach. Each condition (fearful face, neutral face, gray oval) was modeled by a boxcar convolved with a canonical hemodynamic response function. Pairwise contributions of beta parameter estimates for these conditions were compared and represented in contrast images (fearful face versus neutral face, fearful face versus gray oval, neutral face versus gray oval). Data were combined across subjects using a mixed-effects model via FSL's Local Analysis of Mixed Effects (FLAME) tool (Beckmann et al., 2003), with age, gender, education, handedness, ethnicity, and number of response omissions as covariates. Resulting group maps were cluster corrected to control for multiple comparisons using Analysis of Functional NeuroImages (AFNI)'s Alpha Sim Monte Carlo simulations (R.W. Cox, National Institute of Health, Bethesda, Maryland) at a z-threshold of 2.58 and a probability of spatial extent at a p-value of < 0.05. Additional analyses for *a priori* ROIs were conducted in the bilateral amygdala, mPFC, ACC, PHC, fusiform gyrus, and BNST. Effects within these regions were corrected using anatomical masks. All masks were drawn from Harvard-Oxford atlases except the BNST mask, for which no standard mask exists. Thus, for this region, 8 mm spheres were built around the left and right activation maxima (i.e. peak voxels) from the prior report of activation in a threat monitoring task (Somerville et al., 2010).

To investigate regional correlations with clinical symptoms, we interrogated the peak voxel of the activated cluster within each region from between-group contrasts.

Where no group difference existed, peak voxels were identified in the at-risk group map of activation in the relevant condition.

4.2.6 Correlation Analyses

We assessed for relationships between activation in our six *a priori* fear network ROIs (bilateral amygdala, mPFC, ACC, PHC, fusiform gyrus, and BNST), in fearful face and neutral face contrasts (against gray ovals) with eight non-independent measures of clinical severity (GAF, PANSS positive, negative, and general subscales and total scores, and CAARMS severity, frequency, and combined scores) with exploratory correlation analyses. P-values less than 0.05 were considered significant.

4.3 Results

4.3.1 Behavioral Performance

Accuracy on the discrimination task was high and not significantly different for both the at-risk and control groups (mean ± SD: at-risk 93% ± 7%; control 96% ± 4%; Figure 12A). There was no group by condition interaction ($F_{(2,92)} = 1.51$, $p = 0.23$). Both groups were impaired by increasing emotional content (main effect of condition: $F_{(2,92)} = 29.07$, $p < 0.001$). Thus, despite overall high performance, both groups were significantly less accurate at reporting the gender of fearful than neutral faces.

Discrimination task response times showed an overall trend toward slower responses for at-risk than control participants ($F_{(1,92)} = 3.08$, $p = 0.08$) with a significant group by condition interaction ($F_{(2,92)} = 3.93$, $p = 0.03$). Both groups were slowed by

increasing emotional content (main effect of condition: $F_{(2,92)} = 282.59$, $p < 0.001$; Figure 12B).

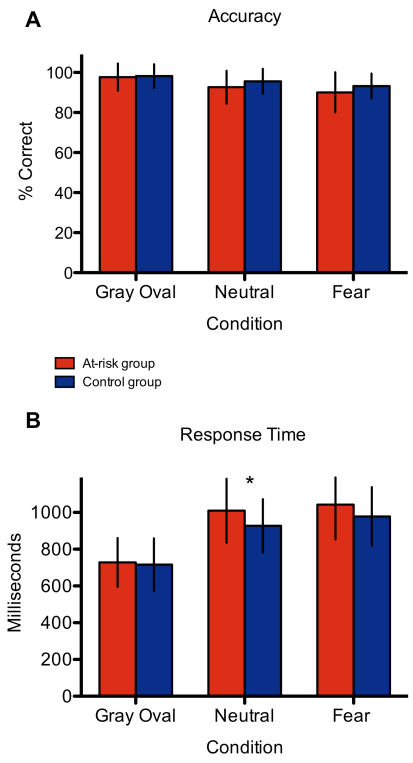

Figure 12: Discrimination task performance of at-risk participants and healthy control subjects during emotional face processing.
***Significant difference ($p<0.05$). Error bars show standard deviations.**

Compared to controls, at-risk participants' response times on gender discrimination were more slowed in the neutral face condition (post hoc t-tests: neutral face $t_{(92)} = 2.40$, $p = 0.02$; fearful face $t_{(92)} = 1.72$, $p = 0.09$; gray oval $t_{(92)} = 0.41$, $p = 0.69$).

4.3.2 fMRI Results

4.3.2.1 Fearful face versus gray oval activations

In the fearful face versus gray oval contrast, both control and at-risk participants engaged regions implicated in fear, facial emotion, and threat processing(Fusar-Poli et al., 2009). These regions included the amygdala, hippocampus, PHC, fusiform gyrus, mPFC (all at whole-brain significance) and ACC ($p<0.05$ corrected within the ACC ROI) in both groups. The BNST was activated only in the at-risk group ($p<0.05$ corrected within the BNST ROI). Neither whole-brain nor ROI analyses revealed significant group differences in areas of interest.

4.3.2.2 Neutral face versus gray oval activations

In the neutral face versus gray oval contrast, both control and at-risk participants engaged regions implicated in fear, facial emotion, and threat processing(Fusar-Poli et al., 2009). These regions included the amygdala, hippocampus, PHC, fusiform gyrus, mPFC (at whole-brain significance) and ACC ($p<0.05$ corrected within the ACC ROI) in both groups. The BNST was activated only in the at-risk group ($p<0.05$ corrected within the BNST ROI). Group contrasts revealed significant differences: At-risk participants showed greater activation relative to controls in the mPFC and ACC, significant at the whole-brain level (Figure 13A).

At-risk participants also showed activation relative to controls in ventral visual stream, including fusiform gyrus and PHC ($p<0.05$ corrected for the combined volume

of MTL and fusiform gyrus ROIs) (Figure 13B) and the BNST ($p<0.05$ corrected within the BNST ROI; Figure 13C).

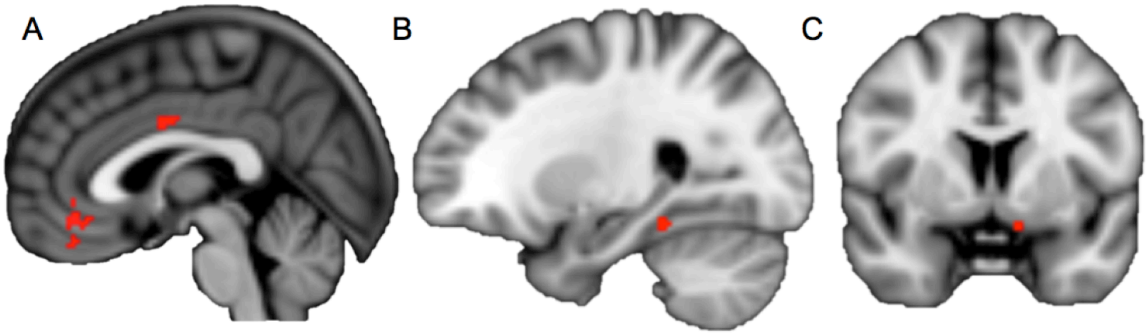

Figure 13: Hyperactivations in response to neutral face stimuli in the at-risk group. Hyperactivations relative to healthy controls were evident in (A) medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) ($p<0.05$, corrected for whole-brain volume); (B) ventral visual cortex including fusiform gyrus and parahippocampal cortex (PHC) ($p<0.05$ corrected for the combined volume of medial temporal lobe (MTL) and fusiform gyrus ROIs); and (C) Bed nucleus of the stria terminalis (BNST)/basal forebrain ($p<0.05$ corrected for the volume of the bed nucleus of the stria terminalis (BNST)/basal forebrain ROI). Images (B) and (C) are masked to show only the activation in the hypothesized brain regions.

4.3.2.3 Fearful face versus neutral face activations

In the fearful face versus neutral face contrast, both control and at-risk groups showed activations in temporo-occipital and inferior frontal gyrus (at whole-brain significance) and within the amygdala ($p<0.05$ corrected within amygdala ROI). Neither whole-brain nor ROI analyses revealed significant group differences in areas of interest

4.3.2.4 Correlations between activation and behavioral measures

Among *a priori* ROIs, amygdala activation in the at-risk group showed correlations with both response time ($r = 0.28$, $p = 0.04$) and accuracy ($r = 0.35$, $p = 0.008$)

on gender discrimination in the neutral face condition. In *a posteriori* regions identified by group contrasts, no correlations with discrimination performance were seen.

Exploratory analyses related eight non-independent measures of clinical severity (CAARMS frequency, severity and combined scores, PANSS and its subscales, and GAF) to activation in six *a priori* fear network regions-of-interest in fearful face and neutral face contrasts (against gray ovals). These analyses revealed the following (uncorrected) significant correlations: ACC and mPFC activations were positively correlated with PANSS positive symptoms in the neutral face condition (Figure 14B and 14C, Table 1). BNST activations were positively correlated with PANSS negative and general symptoms (and consequently PANSS Total), again in the neutral face condition (Figure 14A, Table 1).

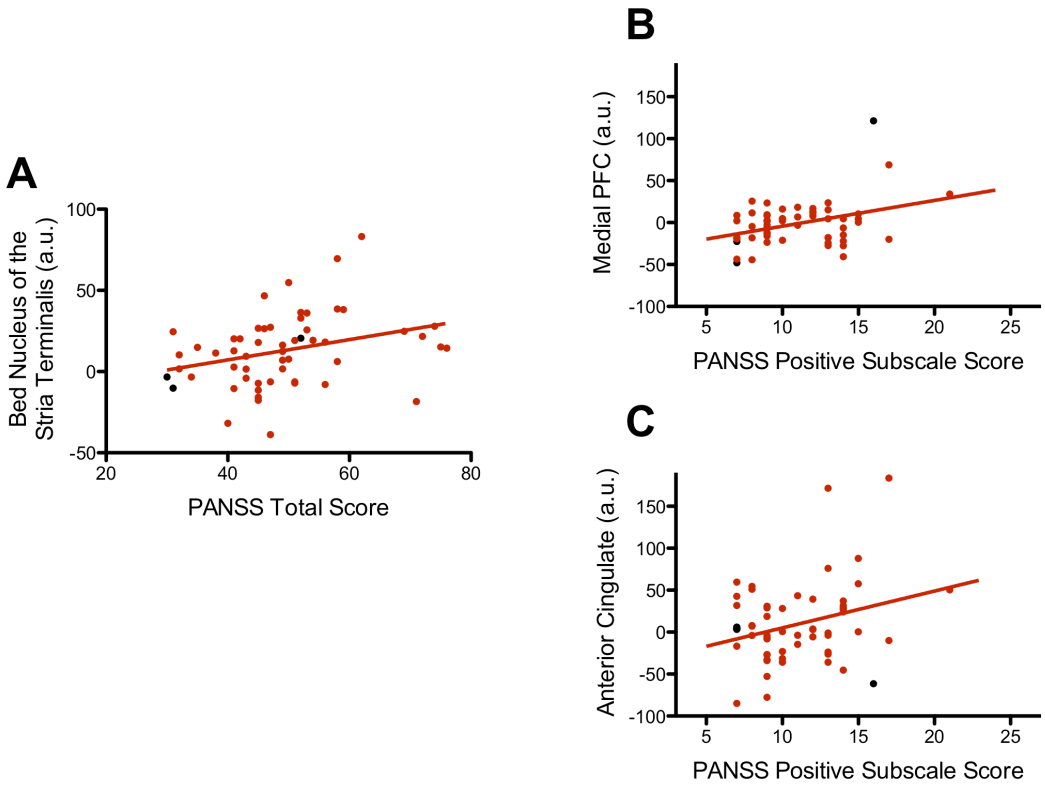

Figure 14: Correlations between clinical severity and activations in response to neutral faces. (A) Increasing PANSS total score correlated with activation in the bed nucleus of the stria terminalis (BNST) (B,C) Increasing PANSS positive symptom score correlated with increasing activation in medial prefrontal cortex (mPFC) and ACC. Data points for participants who have converted to psychosis are represented in black.

BNST activations were also correlated with GAF in the neutral face condition, and with PANSS positive symptoms and GAF in the fearful face condition. Amygdala correlations were more prominent in the fearful face condition, in which amygdala activation was correlated with PANSS positive symptoms, CAARMS (frequency + severity) and GAF scores (Table 1). The overall pattern was thus that greater clinical severity predicted greater fear network activation.

Table 1. Correlations between clinical measures and activations in *a priori* regions of interest in the emotional face processing task (Amygdala, Medial Prefrontal Cortex, Anterior Cingulate Cortex, Parahippocampal Cortex/Fusiform Gyrus, and Bed Nucleus of the Stria Terminalis) in the at-risk group.

Region	Clinical Measure	r	p
Neutral Face vs. Gray Oval Contrast			
Anterior Cingulate Cortex	PANSS Positive	0.281	0.036
Medial Prefrontal Cortex	PANSS Positive	0.360	0.006
Right Bed Nucleus of the Stria Terminalis	PANSS Negative	0.282	0.035
Left Bed Nucleus of the Stria Terminalis	PANSS General	0.269	0.045
Right Bed Nucleus of the Stria Terminalis	PANSS General	0.284	0.034
Left Bed Nucleus of the Stria Terminalis	PANSS Total	0.310	0.020
Right Bed Nucleus of the Stria Terminalis	PANSS Total	0.311	0.020
Left Bed Nucleus of the Stria Terminalis	GAF	-0.319	0.018
Fearful Face vs. Gray Oval Contrast			
Right Amygdala	PANSS Positive	0.365	0.006
Left Bed Nucleus of the Stria Terminalis	PANSS Positive	0.272	0.043
Left Amygdala	CAARMS	0.271	0.044
Right Amygdala	GAF	-0.278	0.040
Right Bed Nucleus of the Stria Terminalis	GAF	-0.273	0.044
Right Parahippocampal Cortex/Fusiform Gyrus	GAF	-0.323	0.016

PANSS = Positive and Negative Syndrome Scale, GAF = Global Assessment of Functioning, CAARMS = Comprehensive Assessment of At-Risk Mental States, frequency + severity

4.4 Discussion

This study examined fMRI activation during fearful and neutral face processing in a large cohort of individuals at risk for psychosis compared to healthy control participants. Although both groups showed the expected pattern of significant fear-network activation during processing of fearful faces, significant group differences in activation and behavior were selectively seen during processing of neutral faces: Among

at-risk participants, amygdala activations were correlated with response time slowing for decisions about neutral faces, suggesting misattribution of emotional salience. Fear-network hyperactivations also correlated with measures of clinical severity and functioning, including measures previously shown to predict progression to psychosis and functional outcome.

The longer decision times shown by at-risk individuals viewing neutral faces offer behavioral evidence of the increased salience of neutral faces for these participants. Such aberrant assignment of salience has been proposed to be a central mechanism underlying the positive symptoms of psychosis(Kapur, 2003). While only at-risk individuals showed this response slowing to neutral faces, emotional content led to slower responses in both at-risk and control participants. Increased decision response times in the presence of emotional distractors in healthy individuals(Hartikainen et al., 2000; Mitchell et al., 2006; Hartikainen et al., 2007; MacNamara and Hajcak, 2009; Weinberg and Hajcak, 2011) has been attributed to the impact of prioritized emotional content on competition for limited attentional resources(Simpson et al., 2000; Vuilleumier et al., 2001; Hartikainen et al., 2012). The disproportionately slower responses for neutral faces seen in at-risk individuals were also correlated with amygdala activation in the neutral face condition. Together, these observations suggest that at-risk individuals may have interpreted neutral faces as more salient because they attributed emotional content to them, just as individuals with schizophrenia have been

shown to assign emotional importance to neutral stimuli(Lakis and Mendrek, 2013). Significantly, active paranoia and susceptibility to visual hallucinations have been shown to be associated with misperception of threat-related emotions in neutral faces(Pinkham et al., 2011; Coy and Hutton, 2012).

Participants were not asked to discriminate emotions in this study for two reasons: first, deficits in emotion discrimination have been previously demonstrated, both in schizophrenia (Kohler et al., 2003) and in those at-risk for the disorder(van Rijn et al., 2010), and second, decision-making about emotion reduces the limbic system hyperactivation(Hariri et al., 2000; Hall et al., 2008) that was our primary prediction. Individuals with schizophrenia consistently show hyperactivation of regions involved in emotional face processing while viewing neutral face stimuli(Holt et al., 2006; Hall et al., 2008; Habel et al., 2010). In the current study, at-risk individuals indeed showed similarly increased activation of threat-detection network ROIs to neutral faces. These patterns included hyperactivations in the BNST, which has been implicated in threat valuation(Mobbs et al., 2010; Somerville et al., 2010), and in mPFC, ACC, and PHC/fusiform gyrus, which all show activation only to threatening faces in healthy controls(Fusar-Poli et al., 2009) but to neutral faces in schizophrenia(Surguladze et al., 2006; Hall et al., 2008; Habel et al., 2010). Together, our findings thus suggest not only aberrant salience but also a bias toward threat detection, consistent with hypervigilance in at-risk individuals. Such patterns of impaired or biased 'predictive perception' have

been posited to represent a primary dysfunction in the at-risk mental state(Keefe and Kraus, 2009; Keefe et al., 2011).

Group differences in response times and brain activation to neutral faces suggest a disruption in processing facial expression but do not directly address emotional state or distress. We further investigated activation of regions implicated in anxiety and fear generation(Kim et al., 2011) identified in prior studies of at-risk populations(Modinos et al., 2010; Gee et al., 2012; Modinos et al., 2012). Consistent with comparisons of amygdala reactivity in those at genetic risk of schizophrenia relative to healthy controls(Rasetti et al., 2009), but contrary to our predictions, the amygdala, while activated in both groups for fearful versus neutral faces, nevertheless showed no significant group difference. However, robust significant group differences emerged in ACC and mPFC when viewing neutral faces. Moreover, we observed individual differences in fear network regions that were correlated with indices of clinical severity and overall functioning, as detailed below.

In both mPFC and ACC, previously shown to be activated by threatening faces in healthy controls(Fusar-Poli et al., 2009) but by neutral faces in schizophrenia (Surguladze et al., 2006; Hall et al., 2008; Habel et al., 2010), activations in the neutral face condition correlated with the positive symptom subscale of the PANSS. This subscale includes items targeting hallucinations, delusions, and paranoia. Significantly, initial high scores on this subscale are significant predictors of transition to

psychosis(Morrison, 2004).

BNST activation in the neutral face condition was correlated with PANSS negative and general but not positive symptoms. PANSS negative symptoms include emotional and social withdrawal, and PANSS general symptoms include anxiety, tension, and social avoidance, among others. These relationships complement the increasing body of work implicating the BNST in threat-monitoring and anxiety, part of a cluster of symptoms that, along with negative symptoms, drive the significant social dysfunction in schizophrenia(Hunter and Barry, 2012). Indeed, BNST activation in the neutral face condition was negatively correlated with GAF scores: more BNST activation predicted decreased functioning. Low GAF scores have also been shown to be strong predictors of transition to psychosis(Yung et al., 2004; Velthorst et al., 2009).

By contrast with BNST and mPFC/ACC, amygdala activation showed correlations that were more robust in the fearful face than the neutral face condition and were less selective in predicting clinical measures. The correlations of amygdala activation to fearful faces with PANSS positive symptoms, CAARMS (frequency + severity) and GAF scores highlight the amygdala's pervasive role in the fear network and its dysregulation in schizophrenia.

In summary, greater fear network activation predicted greater clinical severity, with frontal cortical activations predicting PANSS positive symptoms, BNST activation predicting anxiety and GAF, and amygdala activation showing less specific

relationships with PANSS positive symptoms, CAARMS (frequency + severity) symptoms, and GAF. Whereas amygdala activation was more predictive of clinical measures in the fearful face condition, the BNST, mPFC and ACC were more predictive of clinical measures in the neutral face condition. These associations suggest that functional abnormalities in the fear-network contribute to symptoms and poor functioning even before psychosis onset(Carrión et al., 2011).

Several study limitations should be noted. First, both Asian and Caucasian faces were used as stimuli. Because the standardized Matsumoto and Ekman set contained too few Asian faces, an equal number of Ekman Caucasian faces was included. There were too few per category to analyze selective effects of ethnicity. However, the numbers of Asian and Caucasian faces in each category (fearful, neutral) were balanced, so ethnicity was not a confound.

In addition, it is currently unknown which participants will develop psychosis in the long term, thus another potential limitation is that the study's findings may reflect general psychopathology rather than risk of transition per se. Transition to psychotic disorder is a commonly used outcome measure for studies in at-risk individuals; however, this binarization of outcomes is artificial, and there has been increasing interest in functional outcome as an at least equally important outcome measure. Baseline GAF score has been shown to be a significant predictor of both transition to psychosis(Nelson et al., 2013) and functional outcome(Flyckt et al., 2006). Significantly, abnormal brain

activations in the fMRI task used here significantly predicted scores on this standard scale of psychosocial functioning.

During a two-year follow-up, only six participants in this sample have converted to psychosis. It is not uncommon for recent studies of at-risk subjects to report lower-than-population conversion rates (Yung et al., 2008; Fusar-Poli et al., 2012), partly because study participation can itself be therapeutic, and partly because of lead-time bias (Nelson et al., 2013), with earlier detection of at-risk status leading to longer periods between identification and transition. For this reason, a consensus beginning to emerge is that such predictive analyses could continue to be beyond the reach of even large studies like this one. Thus, while this study cannot identify reliable predictors of psychosis during 'treatment as usual', it provides a large data set for characterizing those at risk. Perhaps more pertinently, it may be that correlations with current symptoms and functioning are the best proxies for those predictors likely to be obtained. Separate from the goal of predicting conversion, studying an at-risk population also offers the opportunity characterize illness-associated dysfunction, while avoiding common illness-associated confounds, like long-term neuroleptic treatment.

One strength of this sample is its size: this is one of the largest functional imaging studies comparing individuals at risk for psychosis and control participants(Fusar-Poli, 2012), as part of the Longitudinal Youth At Risk Study (LYRIKS) led by Singapore's National Institute of Mental Health. Singapore's structured society, small geographical

area, and comprehensive health, military, and educational systems offer multiple advantages for a longitudinal study. Low rates of nicotine, alcohol, and other comorbid substance abuse in Singapore(Verma et al., 2002; Picco et al., 2012; Subramaniam et al., 2012) are other unique advantages.

An additional notable study feature is that it is part of a theoretically-grounded fMRI battery of four tasks targeting stress reactivity, reward anticipation, working memory(Yaakub et al., 2013) and hippocampus-dependent learning. This battery targets memory and motivational systems as potential primary mechansims in the onset of schizophrenia. It is nested within a larger neurocognitive battery that includes standard tests and novel assessments of memory-based predictive perception(Keefe and Kraus, 2009; Keefe et al., 2011). This coherent approach allows tracking of participants across the functional battery and integration of imaging findings with neurocognitive data from a larger sample. For example, here, we specifically interrogated the left anterior insula region that, in the fMRI working memory assay(Yaakub et al., 2013) showed less activation in at-risk individuals than controls; this region was not activated in either group in the current paradigm.

In conclusion, this study demonstrates fear-network hyperactivation to neutral facial expressions in individuals at risk for psychosis. This hyperactivation was associated with the slowed reaction times typical for fearful faces, consistent with attributing emotional content to neutral items. In addition, activations in fear-network

regions were correlated with current clinical severity and functioning, including measures previously shown to predict progression to psychosis and future functional outcome. These findings suggest that functional brain abnormalities associated with dysfunctional threat perception in at-risk individuals may contribute to their decreased resilience, poorer functioning, and increased risk for psychosis onset.

5. General Discussion

Schizophrenia is a complex psychiatric illness hypothesized to result from dopaminergic dysfunction, glutamatergic dysfunction, and dysfunctional stress-reactivity. Prior to the onset of schizophrenia, individuals begin to experience sub-clinical symptoms and decreased functioning during a period referred to as the prodrome. The prodrome is difficult to recognize prospectively, so researchers have begun to study the at-risk mental state, a state that is associated with a high but not inevitable risk of conversion to psychosis in an attempt to identify vulnerability markers for schizophrenia. In the set of experiments described in this dissertation, neurofunctional deficits in reward-anticipation, hippocampus-dependent learning, and stress-reactivity were demonstrated in the at-risk mental state. The altered prefrontal, VTA, and MTL activations that were observed are consistent with previous well-replicated findings in established illness and provide support for an integrated circuit-based model of schizophrenia pathophysiology that incorporates findings from current well-known neurotransmitter and stress-based models, in which the prefrontal cortex, VTA, and MTL play prominent roles. As the abnormalities were seen in the putative prodrome, prior to the onset of psychosis, they offer information about dysfunction associated with vulnerability for the disease and potentially involved in its pathogenesis.

In the remainder of this dissertation, these findings are summarized and interpreted separately and then as a cohesive unit, highlighting connections with current theory, especially with the integrated, circuit-based model of schizophrenia pathogenesis that that was described in the introduction. Implications of findings for understanding the at-risk mental state and early treatment are discussed, and strengths and weaknesses of the set of experiments as a whole are reviewed. The dissertation concludes with ideas for future work that could advance understanding of the development of schizophrenia with potential to delay or prevent this progression.

5.1 Interpretation of Findings

Deficits in reward-system recruitment during reward-anticipation have been demonstrated in individuals with established schizophrenia(Juckel et al., 2006) but only at trend-level for the anticipation of loss-avoidance in small study the at-risk mental state(Juckel et al., 2012). Chapter 2 describes an fMRI study of anticipation of reward and loss-avoidance in which behavior and fMRI activations of at-risk individuals and healthy control subjects were compared. Faster responses for incentivized trials for all participants with no group differences or interactions were demonstrated, suggesting that both groups understood the difference between incentivized and unincentivized trials. At risk individuals showed decreased DLPFC and VTA activation during reward anticipation and decreased medial prefrontal activation during both the anticipation of reward and the anticipation of loss avoidance. NAcc activation during the anticipation

of loss avoidance was inversely correlated with symptom severity, with less Nacc activation predicting increased symptom severity. Together, these findings suggest that at-risk individuals, like individuals with established schizophrenia, fail to adequately recruit the dopaminergic reward system in response to reward-predicting stimuli and that decreased recruitment is associated with increased symptom severity. They are consistent with predictions of the aberrant salience hypothesis for how dopaminergic dysfunction could lead to the clinical symptoms, with dysregulation leading to increased noise in the system that can prevent dopaminergic signals linked to stimuli indicating reward from being detected (Roiser 2008).

Dopaminergic system dysfunction and hippocampal dysfunction are prominent in established schizophrenia and are receiving interest in the at-risk mental state. Chapter 3 describes an fMRI study of hippocampus-dependent learning that involves interactions between the hippocampus, dopaminergic midbrain, and prefrontal cortex. Behavior and fMRI activations of at-risk individuals and healthy control subjects while performing this task were compared. Relational memory deficits were demonstrated in the at-risk individuals**.** Increased DLPFC and hippocampal activation during learning were demonstrated in addition to decreased VTA activation. The decreased VTA activation during learning was correlated with greater clinical severity and decreased performance on a measure of social function. Social function was also predicted by ability to generalize information to new associations. Together, these findings suggest

that at-risk individuals have limited VTA recruitment during learning despite potential compensatory hyperactivations in the DLPFC and hippocampus that predicts symptom severity. The dysfunctional activation of these key regions connecting the dopaminergic and glutamatergic models of schizophrenia during relational learning highlights the major role that deficiencies in learning play in the disability associated with the disease. Deficiencies in cognition, including relational memory, and social dysfunction are two of the primary disabling deficits in schizophrenia. The experiment described in Chapter 3 shows relationships between these deficiencies in the at-risk mental state. It makes an even more interesting discovery that altered activation in prominent regions associated with schizophrenia pathophysiology during a relational memory task also predict social dysfunction, offering an avenue into future studies pathophysiological basis of social dysfunction in both schizophrenia and its prodrome.

Individuals with schizophrenia show increased stress-reactivity and increased activation in fear and threat related regions to neutral stimuli, including neutral faces(Surguladze et al., 2006; Hall et al., 2008; Lakis and Mendrek, 2013). Such hypervigilance may begin to occur prior to the onset of established disease, making individuals vulnerable to disease development. Chapter 4 describes an fMRI study of emotional and neutral face processing in at-risk individuals in which behavioral performance and fMRI activations are compared. Both groups were slowest at male-female discrimination for fearful faces, and the at-risk group was slower than controls in

male-female discrimination for neutral faces. At-risk individuals showed increased engagement of regions involved in fear and threat monitoring in response to neutral faces, including the ACC, mPFC, and BNST In addition, activations in fear and threat related regions were correlated with clinical severity and functioning, including measures previously shown to predict progression to psychosis and future functional outcome. Together, these findings suggest that high-risk individuals process objectively neutral facial expressions the way healthy controls process faces expressing fear. Consistent with the theory that misattribution of salience leads to positive symptoms of schizophrenia(Kapur, 2003), active paranoia and susceptibility to visual hallucinations have been shown to be associated with misperception of threat-related emotions in neutral faces (Pinkham et al., 2011; Coy and Hutton, 2012). The neural activations in threat-related regions in response to neural stimuli during the at-risk mental state fit well with the diathesis stress model of schizophrenia, in which these hyperactivations to neutral stimuli could represent the vulnerability that when exposed to major stressors results in progression to schizophrenia.

5.2 Synthesis of Findings

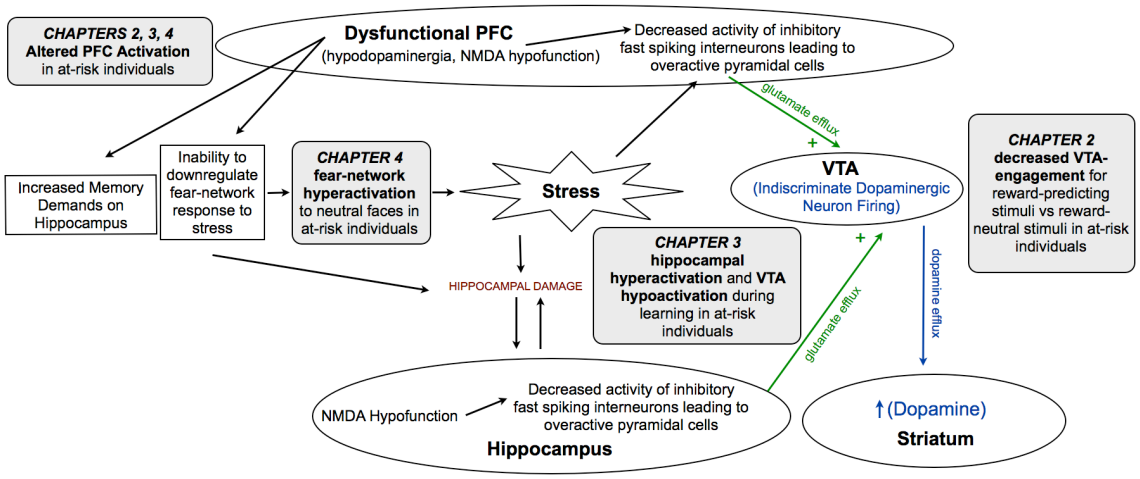

Figure 15. Study contributions to the integrated model of schizophrenia

When considered separately, these studies targeting stress reactivity, reward anticipation, and hippocampus-dependent learning provide insights into task-associated neurofunctional abnormalities in the at-risk mental state in regions predicted by known dysfunction in schizophrenia. When taken together and couched in theory, they provide an integrated picture of the systems-wide neurofunctional pathology that is present in the at-risk mental state. The battery of studies target memory and motivational systems as primary mechanisms in the onset of schizophrenia, with stress hyper-reactivity reflecting decreased resilience and serving as an indicator of vulnerability.

Both the hippocampus-dependent learning task and the reward-anticipation task reveal decreased engagement of the dopaminergic midbrain. This is consistent with aberrant salience models of schizophrenia that suggest baseline dopaminergic hyperreactivity to unimportant events may prevent a signal from emerging from the

noise for salient events(Kapur, 2003; Howes and Kapur, 2009) such as reward cues or items to be associated in memory for later testing. In both tasks, this decreased dopaminergic midbrain recruitment is associated with altered activation in the DLPFC, suggesting the dopaminergic midbrain hypoactivation in the at-risk group may be explained by failures in prefontal regulation of mesolimbic dopaminergic systems during learning and reward-processing. The increased prefrontal activation in the hippocampus-dependent memory study could represent increased glutamatergic neurotransmission in the prefrontal cortex, which would lead to excitation of the hippocampus(Lisman et al., 2010), consistent with the increased hippocampal activation also seen in this study. Alterations in hippocampal activity, due to its prominent role between the glutamatergic and dopaminergic circuits, could then explain the blunted adaptive dopaminergic response in the VTA. While such adaptive dopaminergic system responses are blunted in the at-risk mental state, there is increased putatively mesocortical (mPFC and ACC) activation and activation in other regions of the fear network during the viewing of neutral faces in the stress-reactivity task. This is associated with increased reaction times to neutral stimuli associated with increased amygdala activation, and potentially represents misattribution of emotional salience to the neutral faces. The increased activation in PFC in response to neutral stimuli, when thought of as minor stressors, could represent stress-related activation of glutamatergic neurotransmission in the PFC. Stress-related glutamatergic activation in a dysfunctional

PFC would then lead to increased dopaminergic neurotransmission (Moghaddam, 2002), providing an explanation for how increased distress may lead to increased baseline dopaminergic neuron firing not tied to salience, leading to increased noise in the system and ultimately to positive symptoms of psychosis like delusions and hallucinations.

5.3 Implications of Findings

In addition to providing support for an integrated model for the development of psychosis that ties together the glutamatergic, dopaminergic, and stress-diathesis hypotheses, the neurofunctional abnormalities discovered in this set of studies have the potential to serve as biomarkers for the at-risk mental state for schizophrenia. If predictors can be identified and individuals at risk for the disease can be identified early, disease onset can potentially be delayed or prevented by existing and yet-to-be-developed strategies. At the very least, standard treatment can be initiated earlier to improve outcomes, which worsen with longer periods of untreated illness(Perkins et al., 2005). Specific treatments that could be targeted at the at-risk mental state are suggested by the models supported by the studies in this dissertation. Heightened response to daily stressors could be addressed with cognitive behavioral therapy, which has been shown to decrease severity of symptoms after one year of follow-up in at-risk individuals (Morrison, 2004). Other options for targeting the heightened stress response are inhibitors of hpa-axis activity like mifepristone. This potent antagonist of

glucocorticoid receptors was not effective at improving symptoms of established illness(Gallagher et al., 2005), but this was likely due to the damage that had already occurred based on the increased stress response to benign stimuli that had been occurring at least since adolescence. It has not yet been studied in the at-risk mental state. The hyperdopaminergia leading to the assignment of aberrant salience is another potential target for treatment in the at-risk mental state. Early NMDA hypofunction could be treated early with NMDA glycine-site agonists such as glycine, D-serine, or D-cycloserine, all of which have shown some benefit in established illness. Early-treatment before the onset of disease could potentially prevent some of the downstream effects of glutamatergic dysfunction, namely hippocampal damage. Computerized training to improve cognition (Biagianti and Vinogradov, 2013) during this same period could slow the development of psychosocial dysfunction that being increasingly emphasized as a critical outcome that parallels conversion to psychosis(Carrión, 2013). Preventing this functional decline that is so characteristic of schizophrenia is a target for prevention that is arguably as important as preventing psychosis itself.

5.4 Limitations and Strengths of Included Studies

While the studies in included in this study share important implications, they also share several limitations. It is currently unknown which participants will develop psychosis in the long term. Transition to psychotic disorder is a commonly used outcome measure for studies in at-risk individuals; however, this binarization of

outcomes is artificial, and there has been increasing interest in functional outcome as an at least equally important outcome measure.

During a two-year follow-up, only six participants in this sample have converted to psychosis. It is not uncommon for recent studies of at-risk subjects to report lower-than-population conversion rates (Yung et al., 2008; Fusar-Poli et al., 2012), partly because study participation can itself be therapeutic, and partly because of lead-time bias (Nelson et al., 2013), with earlier detection of at-risk status leading to longer periods between identification and transition. For this reason, a consensus beginning to emerge is that such predictive analyses could continue to be beyond the reach of even large studies like this one. Thus, while this study cannot identify reliable predictors of psychosis during 'treatment as usual', it provides a large data set for characterizing those at risk. Perhaps more pertinently, it may be that correlations with current symptoms and functioning are the best proxies for those predictors likely to be obtained. Separate from the goal of predicting conversion, studying an at-risk population also offers the opportunity characterize illness-associated dysfunction, while avoiding common illness-associated confounds, like long-term neuroleptic treatment.

Studies in this set also share several strengths. One strength of the study sample itself is its size: this is one of the largest functional imaging studies comparing individuals at risk for psychosis and control participants(Fusar-Poli, 2012), as part of the Longitudinal Youth At Risk Study (LYRIKS) led by Singapore's National Institute of

Mental Health. Singapore's structured society, small geographical area, and comprehensive health, military, and educational systems offer multiple advantages for a longitudinal study. Low rates of nicotine, alcohol, and other comorbid substance abuse in Singapore(Verma et al., 2002; Picco et al., 2012; Subramaniam et al., 2012) are other unique advantages.

Using MRI to investigate the neural circuit dysfunction in the at-risk mental state rather than other potential tools for studying human neurophysiology has several advantages. It provides non-invasive recordings from the entire brain in awake individuals with a temporal resolution good enough to capture activations tied to particular events(Huettel, 2012) and an anatomical resolution good enough to show activation in discrete subcortical structures and even midbrain nuclei(Shermohammed et al., 2012; Tomasi and Volkow, 2012). It is a well-established methodology in healthy as well as clinical populations, including schizophrenia, and there is an adequate pool of related historical studies to draw from to provide a scaffolding for findings from newer studies. It is also convenient for use in clinical populations as it requires no contrast agent.

A disadvantage of fMRI is that it does not measure neuronal activity directly(Logothetis and Wandell, 2004). It does, however, measure regional changes in blood oxygenation associated with metabolic demands of neuronal activity, which are coupled tightly enough so that changes in blood oxygenation can serve as a proxy for

neuronal activity(Logothetis, 2008). Another disadvantage is that it shows regional activation that is correlated with task demands and cannot prove causation based on task demands. For this reason, the activation seen during the fMRI tasks in this dissertation cannot be said to be caused by the demands of those tasks (i.e., reward motivation, hippocampus-dependent learning), only that they are candidate regions likely to contribute to these processes.

A notable feature of this set of fMRI studies is that they form the majority of a battery of four tasks targeting stress reactivity, reward anticipation, hippocampus-dependent learning, and working memory(Yaakub et al., 2013). This battery targets memory and motivational systems as potential primary mechansims in the onset of schizophrenia. It is nested within a larger neurocognitive battery that includes standard tests and novel assessments of memory-based predictive perception(Keefe and Kraus, 2009; Keefe et al., 2011).

5.5 Future Directions

The approach of having fMRI studies nested within a larger neurocognitive battery allows tracking of participants across the functional battery providing the opportunity for future analysis integrating imaging findings with neurocognitive data from a larger sample. This is one planned forthcoming direction. Another involves using the fMRI data already collected to probe connectivity between the regions of interest, with a particular interest in probing directional influences using dynamic causal

modeling. Hypotheses to be tested are that the alterations in activation in motivational and fear networks in at-risk individuals may be due to a failure of prefrontal regulation of mesolimbic systems during motivated behavior and learning and of failure of prefrontal regulation of affect and threat-reactivity during viewing of emotional and neutral face stimuli.

A main goal of future analyses, assuming enough individuals convert to psychosis to allow them, will be to characterize those at-risk individuals who develop schizophrenia relative to those who do not convert. This will identify which vulnerability markers are actually associated with transition, providing further evidence that they are involved in the disease process and could be targets for intervention. Having biomarkers that could predict who would develop schizophrenia would be invaluable for life-planning and to provide a springboard for development of interventions that could prevent or delay disease or slow functional decline. At-risk individuals who maintain their at-risk status could also be characterized relative to at-risk individuals who transition out of the at-risk category because they no longer meet criteria, providing potential markers for resilience. A related line of analyses will allow comparisons of initial fMRI scans to fMRI scans after conversion. The study described in chapter 3 of this dissertation demonstrates hippocampal hyperactivation during learning in at-risk individuals, and hippocampal hypoactivation has been demonstrated in schizophrenia(Jessen et al., 2003; Ongür et al., 2006). If such changes in activation

from the prodrome to established illness can be shown in the same individuals, it could provide evidence that constantly increased hippocampal activity might eventually lead to hippocampal damage and thus hypoactivation that is associated with established disease. This would provide clues into neural changes that accompany progression to disease.

Even later in the future, assuming biochemical markers can be identified using studies such as those described in this thesis with follow-up as described in this section, fMRI activations may be used as targets for pharmacological and behavioral interventions as well as interventions like transcranial magnetic stimulation, which is becoming increasingly popular in the treatment of psychiatric disease(Aleman, 2013). Having measurable brain-based indicators of illness to target prior to the onset of illness would revolutionize the field of schizophrenia research and treatment, making biologically based treatment of the underlying problem the priority, rather than the masking of symptoms caused by the underlying problem that is the often unstated goal of current antipsychotic treatment.

5.6 Conclusion

Neurofunctional imaging of the at-risk mental state provides neurofunctional correlates of vulnerability to schizophrenia. Regions identified in the battery of FMRI studies that comprise this dissertation include those that would be predicted by prominent neurochemical and stress-related models, including prefrontal cortex,

dopaminergic midbrain, and hippocampus. The findings when grounded in theory contribute to the pathophysiological understanding of the development of schizophrenia and have treatment implications that could affect disease trajectory. Extension of these studies through the onset of psychosis in a subset of the studied individuals has the potential to identify the dysfunction revealed in these studies as biomarkers of vulnerability. Treatments may be targeted to those biomarkers that are subsequently shown to play a role in disease development, with the potential to significantly alter the life-courses of individuals prone to psychosis.

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Biography

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Publications

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