A Translational Approach to the Neurobiology of Persecutory Ideation in Schizophrenia

A DISSERTATION SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL OF THE UNIVERSITY OF MINNESOTA BY

Melissa Kay Johnson

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Advisor: Angus W. MacDonald III, Ph.D

August 2011

Acknowledgements

In these acknowledgements I thank my advisor, Angus MacDonald, for his mentorship. He has had a tremendous positive influence in my life. He is the most important teacher I ever had. I thank my husband who has supported me financially and emotionally over the past 10 years on this academic rollercoaster. We have grown so much together. I thank Dori Henderson, Madelyn Steen and Edward Patzelt for all of their help and for being such awesome people. I thank Kristen Haut and Rachel Force for their support and friendship. Finally, I thank the NARSAD foundation and Loiuse Francouer for their generous financial support of this project.

Dedication

First, I dedicate this manuscript to my mother who would have been so insanely proud of me. Second, I dedicate this manuscript to my son. I've had so many people comment on how hard it must have been to have a child in graduate school. I honestly don't know what I would have done without him. He gives me purpose and keeps me centered. Having him is the most important thing I have ever done.

Table of Contents

List of Tables

List of Figures

Chapter 1
Introduction

Schizophrenia is a chronic, heritable mental disease with an age of onset in young adulthood that affects about 1% of people worldwide (MacDonald & Schulz, 2009). Schizophrenia has a heterogeneous presentation that includes negative, positive and disorganized symptoms. Schizophrenia's varied symptomology creates challenges in studying its neurological basis. One way to study the neural mechanisms underlying schizophrenia is to narrow the focus to specific symptoms. Positive symptoms, including delusions and hallucinations, are a hallmark dimension of schizophrenia. Persecutory ideation is a relatively homogenous, common, and clinically significant type of delusion in schizophrenia (Appelbaum, Robbins, & Roth, 1999). Because of these characteristics, persecutory delusions are a useful proto-type for studying the neurobiological basis of positive symptoms, and will provide the target symptom for the translational study conducted for this dissertation.

As defined by the NIMH, translational research programs are, "aimed at understanding the pathophysiology of mental illness and hastening the translation of behavioral science and neuroscience advances into innovations in clinical care". Research involving basic cognitive mechanisms underlying observable disorganized symptoms has informed the field of the neurobiological and genetic etiologies of schizophrenia (MacDonald, Becker, & Carter, 2006; MacDonald & Carter, 2003; MacDonald, Pogue-Geile, Johnson, & Carter, 2003). Investigations of Persecutory Ideation have led to several putative underlying cognitive mechanisms including theory of mind, probabilistic reasoning, information processing, and anticipation of threat.

However, the measures used have either been unsuitable for neuroimaging techniques or have resulted in equivocal findings due to lacking specificity. As a result, none of these lines of research has resulted in a single basic cognitive mechanism that merits translation to neurobiology, genetic, and treatment studies of mental illness. In this dissertation I will argue for a new approach to studying persecutory delusions, one that takes inspiration from behavioral neuroeconomics.

Research from the behavioral neuroeconomics and personality literatures can refine our understanding of the possible cognitive and neural mechanisms that underlie persecutory ideation. The field of behavioral neuroeconomics has informed psychology's understanding of social decision-making through the use of the trust game, a variant of the prisoner's dilemma (Poundstone, 1992). The extent to which individuals display off-equilibrium behavior in these games can be related to individual differences in personality and neural processes (Gunnthorsdottir, McCabe, & Smith, 2002; McCabe, Houser, Ryan, Smith, & Trouard, 2001).

The personality literature suggests that distrustful decision-making biases may be affected by two overlapping but unique traits: cynicism and persecution. In response, a group of researchers, including the current author, developed the Minnesota Trust Game (MTG). The MTG is capable of reliably measuring the cognitive mechanism underlying persecutory decision-making biases while controlling for related but confounding constructs. As a result, the MTG is a well-suited paradigm for exploring the neural basis of persecution, a psychological phenomenon that is likely associated with multiple areas of the brain and will be the central tool for exploring this symptom in the current dissertation.

The field of affective neuroscience has studied neurobiological processes related to persecution in both general and psychiatric samples (Amodio & Frith, 2006; Blackwood, 2001; Pinkham, Hopfinger, Ruparel, & Penn, 2008). Findings suggested that deciding if someone is trustworthy involves regions of the brain associated with emotional responses, such as the amygdala and insular cortex. Deciding to trust or not to trust someone requires higher order social cognition such as theory of mind (ToM), a process by which humans attempt to understand the intentions, desires, and beliefs of other people. Deciding to trust someone also requires self-referential processes including the representations of one's own intentions, desires and beliefs. The review of the literature in this manuscript found that there was no specific and reliable theory of mind deficit associated with persecutory ideation. However, the personality literature suggested that persecutory ideation had a uniquely self-referential bias. Through economic decision-making, semantic judgment, facial recognition, and perspective taking paradigms investigators have begun to disentangle the neural bases of theory of mind and self-referential cognitive processes. Key regions of interest for these processes include the ventromedial prefrontal cortex, paracingulate gyrus, orbital frontal cortex and the anterior cingulate cortex. The Minnesota Trust Game's ability to reliably identify a specific decision-making bias associated with persecutory ideation provides an opportunity to investigate the neural basis of persecutory ideation in schizophrenia and add to the field's understanding of social cognition.

1.1 Diagnosis and Symptoms of Schizophrenia

1.1.1 Diagnosis

Over the past 150 years, the heterogeneous symptom presentation of schizophrenia has been debated by some of the best minds in the field of medicine. Both Emil Kraepelin (1856-1929) and Eugen Bleuler (1857-1939) described in great detail the varied symptoms present in schizophrenia (Appendix 1). As a result of the contemporary medical model of mental illness, both men were aware of the heterogeneity's implications for the biology of the disorder. In his book, *Dementia Praecox or the Group of Schizophrenia* (1950), Bleuler wrote that the clinical picture of schizophrenia was so varied that, "the concept of schizophrenia may only be temporarily useful as it may later have to be reduced in the same sense as the discoveries of bacteriology necessitated the subdivision of the pneumonias in terms of the various etiological agents."

As of yet, schizophrenia is still largely treated and studied as a single disease entity. However, psychology and psychiatry's conceptualization of schizophrenia has not been static. Since the original DSM publication in 1952, the DSM has undergone four full revisions and in each revision the diagnostic criteria for schizophrenia have been changed (Appendix 2). As the field begins the fifth revision of the manual the utility of diagnostic categories has been of intense debate.

Of particular relevance to schizophrenia are the polythetic diagnostic criteria. A polythetic diagnosis requires that members of the class have many, but not all criteria in common. For example, in order to meet Criteria A of the schizophrenia diagnosis a patient must have two out of five of the criteria (i.e., hallucinations, delusions, negative symptoms, disorganized speech or behavior, catatonia). One patient can meet criteria with delusions and hallucinations, while another patient can meet criteria with disorganized speech and negative symptoms, resulting in two patients with schizophrenia who have completely non-overlapping sets of psychotic symptoms. If there are different biological etiologies for different schizophrenia symptoms, the signal associated with any one symptom coming from a heterogeneous group of patients would be quite weak.

1.1.2 Dimensions

As a result of the problems caused by current diagnostic methodologies, dimensional descriptors of symptom types have become more common. Using factor analytic methods, Andreasen and Olsen (1982) developed criteria for three subtypes of schizophrenia: Positive, Negative, and Mixed. Later, Andreasen (1995) published data using the Schedules for the Assessment of Negative and Positive Symptoms that showed three main symptom dimensions present in schizophrenia: Positive, Negative and Disorganized. The Negative symptoms of schizophrenia include flattened or blunted affect, avolition, and anhedonia. The disorganized symptoms include disordered thinking as manifested by unusual and/or disorganized speech and behavior. Positive symptoms are commonly referred to as psychosis or reality distortion and include delusions and hallucinations.

The validity of dimensional models of schizophrenia is supported by their relationship to neural systems, familial risk, premorbid features, onset and course (Carpenter, 2007; Carpenter, Heinrichs, & Wagman, 1988; Dikeos et al., 2006). For example, psychotic symptoms in a nonclinical sample represented a genetic liability to schizophrenia spectrum disorders (DiLalla & Gottesman, 1995). Within twin pairs discordant for schizophrenia, non-affected twins' scores on personality traits ostensibly related to positive and negative symptoms (i.e., Alienation, Absorption, and Social Closeness from the MPQ) showed a significant positive correlation with probands' scores. Positive symptoms have also exhibited predictive validity (Poulton et al., 2000). Children from the Dunedin sample who self-reported strong psychotic symptoms at 11 years old were more likely to develop schizophreniform disorder at 26 years old. The dimensional model of psychiatric problems has gained so much steam that the DSM-V has developed a "task force" for developing reliable dimensional categories to be used in research settings.

1.1.3 Persecutory Ideation

Within the category of positive symptoms, persecutory ideation is one of the most common and pervasive manifestations of psychosis (Appelbaum, et al., 1999). This finding has been replicated across cultures, in both developed and developing nations (Ndetei & Vadher, 1984; T Stompe et al., 1993). The presentation generally involves pervasive beliefs that the individual is being spied on, plotted against, or harmed by an individual or group of individuals with malicious intentions. In a clinical sample of 25 patients with psychotic disorders, the delusions of 19 patients involved either another person, a group of people, an organization, or everybody (D. G. Freeman, P.A., 2004). Of the remaining 6, 5 believed their persecutors were devils, sprits, or forces and one believed the persecutor was an alien. The content of the delusions ranged from a vague threat from an unknown persecutor, "Three or four people are out to get her", to a bizarre attack from a specific person, "A neighbor has cast a black magic spell on him so he is punched at night." The anticipated threat in these cases was largely physical, psychological, social, or financial.

Persecutory beliefs are associated with a host of negative outcomes. For example, persecutory beliefs, rather than a diagnosis of schizophrenia, predicted violence in the Dunedin birth cohort (Arseneault, Moffit, Caspi, Taylor, & Silva, 2000). Persecutory ideation has been associated with poor medication compliance (Owen, Fischer, Booth, & Cuffel, 1996; Wilson & Enoch, 1967) and poor functioning in the social domain (Pinkham, Hopfinger, Ruparel, et al., 2008) that people with persecuted beliefs reported increased rates of adverse events such as victimization and discrimination (Fuchs, 1992; Janssen, Hanssen, Bak, de Graaf, & Vollenberg, 2003; Mirowsky & Ross, 1983). Finally, Persecutory beliefs predicted suicidality in patients suffering from schizophrenia and mood disorders (Bottlender, Jager, Strauss, & Moller, 2000; Saarinen, Lehtonen, & Lonnqvist, 1999)

1.3 Measures of Persecutory Ideation in the Schizophrenia Literature

As a result of persecutory ideation's clinical significance, many investigators have attempted to identify constructs that are etiologically related, including theory of mind, attributional biases/self-esteem, probabilistic reasoning biases, information processing biases, and anticipation of threat. Theory of mind (ToM) can be defined as the ability to impute mental states such as thoughts, beliefs and desires, to others (Premack, 1978). Overall, ToM deficits do not appear to be unique to persecutory delusions. For example, Corcoran (R. Corcoran, Mercer, & Frith, 1995) found that in comparison to normal and psychiatric controls, persecuted schizophrenia patients had difficulty on a "hinting" task in which participants were asked to infer intentions based on the indirect speech of others. However, schizophrenia patients with negative features and incoherent speech showed the worst performance. Frith (2004) has suggested that patients with persecutory delusions do not entirely lack the ability to take on another's perspective. In fact, they may 'over-mentalize' and incorrectly impute negative intentions to others. One problem researchers have encountered when measuring ToM is the high cognitive load of the experimental paradigms. This idea is consistent with the findings of Bentall et al (2009), a cross-diagnostic study, in which a factor analysis revealed three main latent factors that contribute to persecutory ideation: cognitive performance, paranoia, and depressive thinking style. Performance on the theory of mind task loaded strongly onto cognitive performance (r=.72).

Probabilistic reasoning deficits, known as 'Jumping-to-conclusion biases', have also been considered as a mechanism underlying delusional thinking (Hemsley & Garety, 1986). In one probabilistic reasoning task, participants were presented with two jars, one containing mostly black and one containing mostly white beads. Experimenters told participants to draw as many beads as they liked before determining which jar contained mostly white beads. Results indicated that deluded patients, either persecuted or grandiose, selected fewer beads than comparison subjects in order to make their prediction. However, the most recent study found differences between control subjects and schizophrenia patients, but did not find differences between deluded and non-deluded patients. This suggest that the paradigm was measuring a generalized deficit associated with schizophrenia, rather a symptom-specific mechanism (Menon, Pomarol-Clotet, McKenna, & McCarthy, 2006). Much like ToM, Bentall et al (2009) found that jumping-to-conclusion biases loaded onto a cognitive performance factor (r=.47).

Multiple studies of persecution have used an interview that assesses heightened anticipation of threat. Participants are read multiple social interactions (seven negative, seven neutral, seven positive) and asked to rate the likelihood of each event occurring to themself and to another unspecified person in the next month using a seven point Likert-type scale ranging from “not at all likely” to “very likely” (Bentall, et al., 2009; R Corcoran et al., 2006; S Kaney, Bowen-Jones, Dewey, & Bentall, 1997). Kaney (1997) found that persecuted patients, with and without depressive symptoms, predicted a greater likelihood of negative events. Corcoran (2006) also asked participants about their experiences in the past month as an operationalization of an availability heuristic (Kahneman, 1979). In an omnibus regression past negative events significantly predicted an increased likelihood of future negative events in patients with persecutory delusions. This finding was not supported in depressed patients. Interestingly, the presence of current persecutory delusions did not make a separate contribution to the prediction of threatening future events. Finally, of the three latent factors, cognitive performance, paranoia, and depressive thinking style, Bentall (2009) found that anticipation of threat was specifically related to paranoia (r=.85). Taken together these findings suggest that patients with persecutory delusions are more likely to anticipate threatening events in their future. The authors suggest that this is in part due to their perceived experience of past negative events. The similarity of the findings in the currently and remitted paranoid patients suggested that the underlying mechanism is relatively stable across changes in symptomatology.

In summary, the research reviewed in this section provides insight into potential mechanisms underlying persecutory ideation; however most of the paradigms used have been unable to produce reliable results with adequate specificity. The anticipation of threat interview appears to be the most reliably associated with persecution. Therefore, a complete model of persecutory ideation should take into account the importance of perceived threat. The anticipation of threat interview does not bring the field closer to a translational model of persecutory ideation because, as a measure, it lacks the ability to elicit in-vivo behavior related to persecution. Persecution manifests behaviorally in social interactions involving trust, as evidenced by persecuted patients' tendency to distrust healthcare providers (Owen, et al., 1996). The following section outlines how a multi-dimensional approach that uses personality research on trust to inform cognitive paradigms from the behavioral economics can lay the groundwork for a promising translational model of persecution.

1.3 A Translational Model of Persecutory Delusions

1.3.1 *Translational Models in Schizophrenia*

The translation of cognitive paradigms taken from basic science research has been a successful method for understanding the biological mechanisms that underlie specific psychological phenomena in psychiatric illnesses. The NIMH has a translational research area in the Adult Psychopathology and Psychosocial Intervention Research Branch. This area emphasizes, "studies that combine approaches from neuroscience and behavioral science to elucidate the role of psychosocial factors in the alterations of brain functioning associated with mental disorders and to produce integrative models of risk, disorder, and recovery". Experimental paradigms designed to tap a putative mechanism of interest are usually piloted in undergraduate samples until optimally parameterized. Once effects have been reliably obtained, experiments can be used in neuroimaging designs, patient populations, and genetics studies. Eventually, the utility of the findings in treatment can be tested in clinical trials. Studies of executive functioning deficits in schizophrenia are an excellent example of successful translational research program in the cognitive neuroscience of schizophrenia.

Executive functioning can be described as self-regulatory skills that affect the individual's planning, flexibility, generation of information, inhibition of impulses, and working memory. Given the presentation of disorganized symptoms, executive functioning has been considered an excellent etiological mechanism of interest. However, executive functioning is a diverse construct composed of many sub-processes, including context processing. MacDonald and Carter (2002) described context processing as the representation of behaviorally relevant information ("context") to support adaptive responses when overcoming competing responses. Cohen and Servan-Schreiber (1992) used a computational modeling to show that context processing, as measured by a continuous performance task (the AX-CPT), could be etiologically related to disorganized symptoms of schizophrenia.

Context processing paradigms have shown a specific deficit in schizophrenia patients and a relationship between context processing and disorganized symptoms (Barch, Carter, MacDonald, Braver, & Cohen, 2003; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Kerns & Berenbaum, 2002). The AX-CPT, and closely related paradigms, have been used to identify context processing as a potential endophenotype for schizophrenia that may have its neural basis in the dorsolateral prefrontal cortex (MacDonald, et al., 2006; MacDonald & Carter, 2003; MacDonald, et al., 2003). Finally, context processing paradigms have been used in a treatment study to investigate changes in neural activity associated with Cognitive Remediation as compared to Cognitive Behavioral Social Skills Training (Haut, Lim, & MacDonald, 2010).

The process of identifying cognitive mechanisms underlying manifest symptomatology is non-trivial. A cognitive mechanism of interest must first be successfully operationalized through the development of an experimental measure that is parameterized to maximize sensitivity and specificity. Once the mechanism and measure have been established in healthy samples, investigators move onto other levels of inquiry. A major hurdle in the process of translating paradigms from healthy to schizophrenia samples is the difficulty level of the experiment. For example, a measure may achieve predicted results in undergraduate samples, but fail miserably in patients because of floor effects associated with poor performance. As a result, experimental paradigms must be carefully modified to maximize patient task-comprehension while still maintaining their construct validity. The task is not insurmountable. Luck and Gold (2008) reported that a team of clinical and basic science researchers at multiple sites have engaged in over 15 such translations over the past 7 years.

As shown by the study of context processing, the translational method is a powerful tool for relating manifest symptoms to its underlying biology. However, few studies have formally applied a translational method to the dimension of positive symptoms. This may in part be due to the perception that positive symptoms are qualitatively different from the normal human experience. As a result, identifying a basic mechanism is, on the surface, counterintuitive. However, there is evidence that the distribution of certain psychotic symptoms is more normal then one might expect.

Allardyce et al (2007) reported that hallucinations and delusions had a continuous distribution in nonclinical samples with prevalence rates ranging from 4% to 17.5%. Persecutory Ideation may have an even wider distribution than other types of positive symptoms. In one study 1,202 men and women from the general population ranging from 17-61 years old completed an online survey containing the Paranoia Checklist (D. Freeman et al., 2005). While the endorsement rate for many items was relatively low there was a surprisingly high rate of endorsement to many items. For example, 52% of people reported that once a week they thought, "I need to be on my guard against others" and 42% of people surveyed reported that once a week they thought, "There might be negative comments being circulated about me". These results suggest an adequate presence of Persecutory Ideation with which to study a cognitive mechanism using translational methods.

1.3.2 *Developing a Cognitive Model of Persecutory Ideation: Findings from the Personality Literature*

Trust, a construct ostensibly related to persecution, has been measured by a variety of personality inventories. Within the Five-Factor Model, trust is similar to the suspicious-trusting and cynical-gullible dimensions, both of which load onto Agreeableness-Antagonism (McCrae & Paul T. Costa, 1987). Rotter's Interpersonal Trust Scale (Rotter, 1967) conceptualized interpersonal trust as, "an expectancy held by an individual or a group that the word, promise, verbal or written statement of another individual or group can be relied upon". Heretick developed a trust scale based on the assumption that developing expectancies of other's motives is a fundamental aspect of trust (Heretick, 1981).

Work using The Minnesota Multiphasic Personality Inventory represents the best understanding of how distrust relates to psychopathology (Hathaway & McKinley, 1940). The MMPI-based Cook-Medley Hostility Scale (HO) was originally developed to assess "a person's ability to work harmoniously and effectively with a group, to establish rapport with others, and to maintain group morale" (Cook & Medley, 1954; Han, Weed, Calhoun, & Butcher, 2000). The HO Scale was predominantly used in health outcome studies of coronary heart disease (CHD) because of anger's negative impact on health (Han, et al., 2000). A factor analysis of data collected from 1002 men and women revealed two underlying components in the HO Scale: Cynicism and Paranoid Alienation. Cynicism from the HO Scale correlated strongly with the Cynicism Content scale (r=.91), while the Paranoid Alienation factor correlated with the Psychoticism/Infrequency scale (r=.66) (Costa, Zonderman, McCrae, & Williams, 1986). Both factors correlated with Neuroticism.

Currently on the MMPI-2, high to very high scores on the clinical Paranoia (Pa) scale were associated with frankly psychotic delusions including ideas of reference, persecution, and grandeur (Butcher, 2000). High scores on the Cynicism (CYN) content scale from the MMPI-2 are associated with misanthropic thoughts and the belief that other people are honest predominantly to avoid punishment (Butcher, 2000). In the MMPI-Restructured Format scales, Tellegen (2003) showed that when factoring out variance associated with general demoralization, the Paranoia scale from the MMPI-2 dropped out and the Cynicism and Persecution scales surfaced. Individuals high on Cynicism believed others look out for themselves and exploit others. They endorsed questions like, "I think most people would lie to get ahead", or "Most people will use somewhat unfair means to gain a profit or an advantage rather than lose it." Individuals high on Persecution had self-referential ideas and believed that they were being mistreated and picked on. They endorsed items like, "Someone has it in for me" and "I feel like I have been punished without cause." Most recently, this finding was replicated in a separate sample of undergraduate men and women in the development of the TRiCAM Trust Scale (n=661), using items from the Schizotypal Personality Questionnaire (Raine, 1991), the Alienation subscale from the Multidimensional Personality Questionnaire (Patrick, Curtin, & Tellegen, 2002; Tellegen & Waller, 2008) and Rotter's Interpersonal Trust Scale (Rotter, 1967).

Taken together these findings suggest that both cynicism and persecution involve the expectations of another person. However, cynicism is predominantly other-regarding, whereas persecution is self-referential. The implications of this conclusion are important to understanding persecutory ideation. First, it is inaccurate to consider persecution a more extreme form of distrust. It is more accurate to say that there are two forms of distrust, cynicism and persecution. Second, an overlapping but unique cognitive and neural mechanism likely drives the manifestation of cynical and persecuted traits. Finally, given that Paranoid Alienation (HO) is closely related to the Psychoticism/Infrequency content scale, it would seem that the mechanism underlying this type of distrust would be closely related to persecutory ideation in schizophrenia. As a result, a cognitive model of persecution based on trust must be able to measure persecution separate from cynicism.

1.3.3 Developing a cognitive model of persecutory ideation: findings from the decision-making literature

Researchers in the field of social and clinical psychology have successfully harnessed decision-making paradigms drawn from behavioral economics to measure individual differences in traits like Machiavellianism, impulsivity, and risk aversion (Gunnthorsdottir, et al., 2002; Madden, Petry, Badger, & Bickel, 1997; Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003; A. Sanfey, 2007). In the trust game, a type of decision-making paradigm similar to the prisoner's dilemma (Poundstone, 1992), a first mover typically decides between an *assured payoff* and the possibility of a greater or lesser payoff depending on the choice of an anonymous second mover. The second mover can then decide to reciprocate the first mover's trust by choosing the *mutual reward* or take a greater amount for himself, typically referred to as the *temptation*. If the second mover selects the *temptation*, the first mover is left with the *adverse payoff*, an amount usually less than the *assured payoff*. There are many versions of the trust game; two commonly used versions are the investor and ultimatum games.

In the investment game two players interact to determine how to divide a sum of money. The first mover can transfer none, some, or all of the money to the second mover with the hope that the second mover will transfer funds back. The first mover is motivated to transfer money to the second mover because the funds are multiplied by some factor during the transfer. If the first mover does transfer funds, the second mover can transfer none, some or all of the multiplied funds back. From a Game Theory perspective, in a one-shot exchange a rational first mover should transfer no money to the second mover based on the assumption that second movers will always act to maximize their own gains. However, first movers have often displayed off-equilibrium behavior by passing non-zero sums to the second mover (Berg, 1995).

Similar to the investment game, the ultimatum game involves two players interacting to determine how to divide a sum of money. The first mover proposes how to divide the sum between the two players, and the second mover can either accept or reject this proposal. If the second mover rejects, then neither player receives anything. If the second mover accepts, the money is split according to the first mover's proposal. The use of the ultimatum game has provided insight into moral beliefs about punishment and their neural underpinnings through the seemingly strange phenomena that low offers made by a human were rejected at a significantly higher rate than offers made by a computer. (A. G. Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). The inclusion of a non-human condition allowed the investigators to isolate punishing behavior while controlling for the general negative emotionality associated with a sub-par offer.

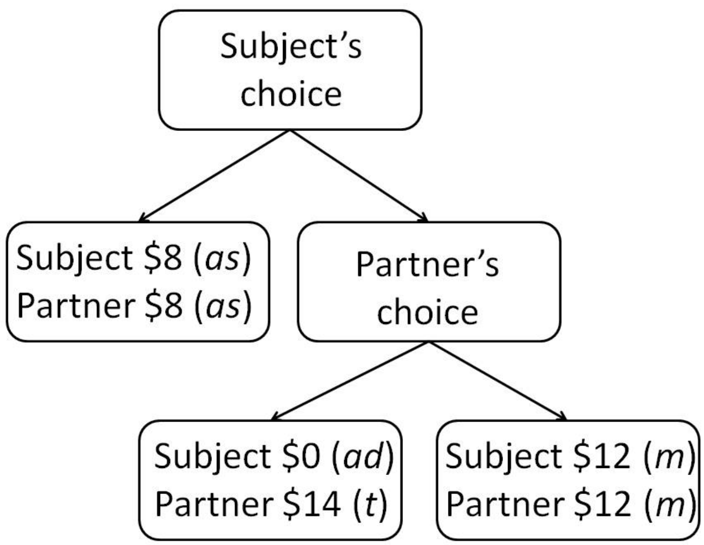
In another modification of the trust game, Bohnet and Zeckhauser (2004) used both human and non-human decision agents wherein the first mover was asked to decide between an *assured payoff* of $10 and the possibility of a greater or lesser payoff depending on the choice of an anonymous second mover or chance. If the first mover chose to trust the second mover, the second mover would have a choice between $15 and $22. If the second mover chose $15 for himself then the first mover would also receive $15 (*mutual reward*). However, if the second mover chose $22 (*temptation*) for himself, the first mover would be left with only $8 (*adverse payoff*). In the chance condition, the first mover decided between an *assured payoff* of $10 and the possibility of a greater or lesser payoff depending on chance.

The results showed that subjects were more likely to select the *assured payoff* of $10 when the second mover rather than chance determined the secondary decision. The authors suggested that this demonstrated a fear of betrayal. The first mover anticipated that the second mover would be tempted to selfishly choose $22. Through the use of the $22 *temptation*, the experimental circumstances mirrored the real life process of weighing the pros and cons of trusting another person who had a motive to betray the subject. From a rational economics perspective, the first mover should have only trusted the second mover when the *adverse payoff* was greater than the *assured payoff* because the second mover would always act to increase his payoff (i.e., choose the *temptation*). So, under the conditions when the *adverse payoff* was less than the *assured payoff*, the choice of the first mover not to trust the second mover indicated 'rational mistrust'.

The Minnesota Trust Game was developed to measure a decision-making bias that would parallel persecuted thinking while controlling for related but confounding constructs including Rational Mistrust and Risk Aversion (M.K. Johnson, Rustichini, & MacDonald, 2009) . In a trust game similar to those discussed in this manuscript, general aversion to risk was identified as a component of the decision to trust (Eckel & Wilson, 2004). In the MTG, risk-aversion was operationalized similarly to the chance condition in Bohnet and Zeckhauser (2004). The authors also identified the need to control for the processes related to rational mistrust. This was operationalized similarly to the betrayal condition in Bohnet and Zeckhauser (2004). Finally, persecution was understood as the belief held by the first mover that the second mover will *disadvantage himself in order to disadvantage the first mover*. In other words, we hypothesized that in an economics framework, a persecuted first mover would believe that the second mover would ascribe utility to causing the first mover harm. This stands in direct contrast to rational mistrust in which the first mover believes that the second mover will act solely in his or her best interest.

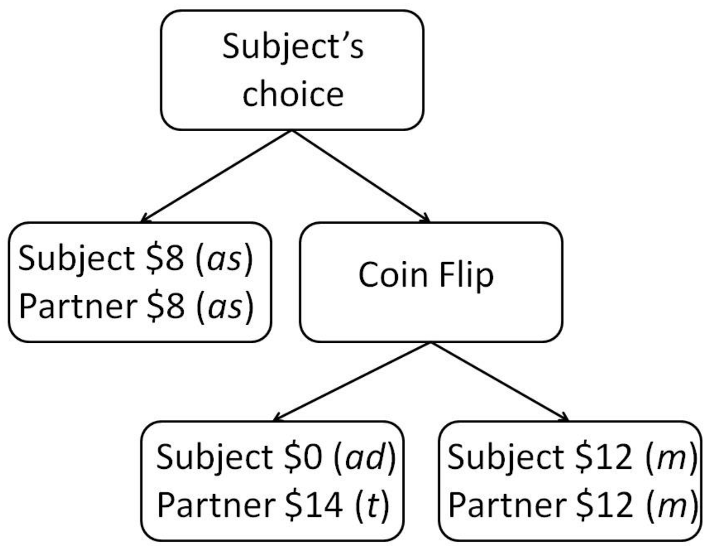
The Minnesota Trust Game contained two main sub-games, Other Player and Risk Aversion. Within the Partner sub-game there were two conditions (Figure 1), the Rational Mistrust condition and Suspiciousness.

Figure 1. *Decision-tree for one trial of the Rational Mistrust condition of the Other Player Game.*



Similar to Bohnet and Zeckhauser (2004), we operationalized Rational Mistrust as choosing the lesser *assured payoff* when the anonymous second mover had a monetary incentive to choose the *temptation* over the *mutual reward*, therefore leaving the participant with the *adverse payoff*. In the Rational Mistrust condition the *temptation* was a larger dollar value than the *mutual reward*. In the Suspiciousness condition the *mutual reward* was a larger dollar value than the *temptation*. Thus, suspiciousness was operationalized as choosing the lesser *assured payoff* even when the second mover has no monetary incentive to select the *temptatio*n and leave the participant with the *adverse payoff*. The Risk Aversion conditions paralleled the Rational Mistrust and Suspiciousness conditions, but differed in that the participant chose between the *assured payoff* and allowing a coin flip to determine the payoff (Figure 2).

Figure 2. *Decision-tree for One Trial of the Risk Aversion 14 Condition*



Thus, choosing the *assured payoff* in this game indicated aversion to risk. The *adverse payoff* varied within each condition, creating varying levels of risk as a means to create individual differences in switch-points.

Subjects' decision-making behavior indicated that they were sensitive to the task manipulation in the hypothesized manner. The level of *temptation* significantly modulated decision-making when the *decision-agent* was the partner, but not the coin, such that subjects were more opportunistic when the *temptation* equaled $10. Subjects made more conservative decisions as their own potential losses increased, as indicated by choosing the *assured payoff*. We observed the predicted three-way interaction such that the impact of the *adverse payoff* on decision-making depended on both the type of *decision-agent* and *temptation*. These results suggest that the Minnesota Trust Game is capable of separately measuring patterns of decision-making associated with suspiciousness, rational mistrust, and risk aversion.

The three-way interaction of *Alienation*decision-agent*temptation* established the specificity of the relationship between *Alienation* and the Suspiciousness condition. *Alienation* predicted decision-making only when the decision-agent was the partner and the *temptation* for the partner to leave the subject with the *adverse payoff* was low. The two-way interaction of *Harm Avoidance*decision-agent* demonstrated that *Harm Avoidance* predicted decision-making in the Risk Aversion but not Other Player conditions. These findings suggest that persecutory ideation is not simply an aversion to risk, but a particular type of interpersonal interaction that can be operationalized as a unique decision-making bias.

In summary, persecutory ideation is a type of clinically significant positive symptom in schizophrenia that, in an attenuated form, is relatively well represented in the general population. As a result, it is ideally situated to serve as a prototype for cognitive models of other positive symptoms. Results from the Minnesota Trust Game have reliably shown a specific relationship between measures of persecuted personality and behavior in the Suspiciousness condition. The next section outlines brain regions that have been reliably activated in paradigms designed to measure social cognition. Special attention will be paid to studies that are ostensibly related to persecuted thinking including anticipation of threat as it relates to trust, theory of mind, and self-referential thinking.

1.4 Application of Current Neurobiological Findings to Persecutory Delusion

1.4.1 The Amygdala and Oxytocin

The neural basis of making the decision to trust someone has been the target of much research and appears to involve a wide-ranging neural network. One area of interest is the amygdala, a region that has reliably been associated with fear responses to threatening stimuli (R. Adolphs, Tranel, D., & Damasio, A.R., 1998). Using a faces-rating task, Winston et al. (2002) asked a sample of 16 healthy men and women to rate a collection of 60 gaze-forward pictures taken of high school and university students. The faces had been previously rated as neutral on expressions of happiness and anger, but either high or low on trustworthiness. This was done to control for general biases associated with these expressions and trustworthiness ratings. For half of the experiment participants were asked to rate whether the faces were trustworthy (i.e., would you trust this person with a month's salary?) and in half of the experiment participants were asked to rate if the person in the image was a high school or university student. Results indicated a main effect of untrustworthiness in bilateral amygdala with the right amygdala particle surviving correction for facial emotion. One interpretation of this finding is that the amygdala determines trustworthiness by detecting the level of risk associated with another person.

The role of the amygdala has been investigated in schizophrenia patients with persecutory delusions (Pinkham, Hopfinger, Ruparel, et al., 2008). Paranoid patients rated faces as less trustworthy than non-paranoid patients and controls. Paranoid patients demonstrated reduced activation in a proposed network underlying social judgments including the amygdala, fusiform face area, and ventrolateral prefrontal cortex. In two other studies using faces, participants were asked to judge the gender of a set of fearful and neutral faces while undergoing fMRI and skin-conductance procedures (Williams et al., 2004a; Williams et al., 2007). Paranoid patients showed less activation to fearful faces than controls and non-paranoid patients despite increased arousal as measured by skin conductance.

Research has implicated oxytocin in the decision to trust. Oxytocin is a neuropeptide associated with a variety of pro-social behaviors including pair bonding, maternal care, sexual behavior, and the ability to form normal social attachments. Oxytocin has also been shown to modulate activity in the amygdala, particularly in response to fearful stimuli (Huber, Veinante, & Stoop, 2005; Kirsch et al., 2005). During a variant of the trust game investors who were given intranasal oxytocin showed increased trust as manifested by higher monetary transfers to the trustee (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). This same pattern was not found when the investor was playing a parallel game of risk. Additionally, there was evidence that oxytocin is relatively specific to trust as opposed to prosocial behaviors in general. Namely, oxytocin was not related to increases in trustee back transfers.

The role of the amygdala and oxytocin in decisions involving trust suggests a dynamic relationship between approach and avoidance systems. The amygdala may act to signal a potentially fearful situation such as taking a risk to trust another person. In a complementary fashion, oxytocin may mediate activity in the amygdala in order to allow approach behaviors when appropriate.

1.4.2 Higher-order cognitive regions associated with trust & persecution

The field of behavioral economics has directly investigated trust using functional neuroimaging and decision-making paradigms. Other neuroimaging research has studied concepts related to trust including thought of others' intentions (Theory of Mind) and thoughts of one's own intentions. Taken together, these lines of research have identified multiple regions in the medial frontal cortex (MFC) ranging from the cingulate to the orbital frontal cortex as areas of interest in social cognition. Over the next several sections of this manuscript, I will review a portion of this research as a means of identifying regions of interest for the Minnesota Trust Game. I will begin with economic decision-making, theory of mind, self-reflection and finally studies contrasting theory of mind and self-reflection.

1.4.2.1 Economic Decision-making Studies

In a study of conditional and unconditional trust, Krueger (2007) used a trust game to explore how brain activity changed over the course of multiple trusting exchanges (Table 1). Forty-four participants, twenty-two pairs, were scanned at the same time and provided with real-time feedback regarding another player's choices. The pair members alternated between playing the role of the first mover and the second mover. The analyses were split into two stages. The first stage was referred to as 'trust building' and the second stage was referred to as 'trust maintenance'. The authors also divided the participants into groups of defectors and non-defectors. The non-defector group was comprised of pairs who never betrayed their partner as the second mover. Participants in the defector group experienced some defection during the experiment.

Behavioral results showed that non-defectors had a higher rate of trusting decisions and displayed faster reaction times as compared to defectors. Additionally, non-defectors tendency to trust as the first mover increased over time, whereas the opposite was true for defectors. The imaging results showed a main effect trust > control in the Paracingulate Cortex (PcC). In the PcC, parameter estimates during the trust building stage were significantly higher for non-defectors as compared to defectors. This relationship reversed in the trust maintenance stage when the parameter estimates were higher for defectors. The authors suggest that the non-defectors' "upfront" work in the PcC allowed them to develop unconditional trust with their partner, resulting in less mentalizing during the trust maintenance phase. Conversely, those in the defector group experienced a relative increase in the PcC as they attempted to integrate their partners' defections into their mentalizing of their partner.

In a study of cooperation, McCabe (2001) used a trust game to show differences in MFC activation associated with different decision-making strategies (Table 1). In this study, the first mover chose between two options: 1) taking a chance to earn more money for both players by trusting the Other Player to decide, and 2) taking a lesser assured payoff for both players. The second mover then also chose between: 1) taking a mutually beneficial payoff, and 2) taking a payoff that resulted in a higher payoff for the second mover. Cooperation was operationalized as choosing option 1 as either first or second mover. Twenty-four participants took part in the study; twelve played the game in the scanner while the other twelve played the complimentary game in the control room. The role (first or second mover) was counterbalanced across the study. The trust game used in this study included a control condition in which participants were faced with a parallel decision involving a computer instead of another person. The experimenter explained to participants that when the computer played the role of the first mover it always chose to 'trust' the other player. When the computer played the second mover, it played a fixed probabilistic strategy. During 75% of the trials the computer's choice would result in a mutually advantageous payoff. However, during 25% of the trials the computer would choose the payoff that resulted in the adverse payoff for the first mover.

The imaging analysis in this study evaluated neural activity associated with the time period 1.5 seconds before the results of the game were presented, regardless of whether the participant was the first or second mover. As a result, the authors suggested that the identified activity was associated with predicting and understanding the cooperative intentions of another player. The human > computer contrast indicated that each of the six participants with high cooperation scores showed a significant increase in several regions of the MFC, whereas none of the low cooperators showed this pattern of activity. In a group analysis of cooperators, the human > computer contrast showed differences between conditions in BA 10 (no coordinates provided). Specifically, the trials involving a human showed an increase in activity, whereas computer trials showed a decrease. The same contrast in non-cooperators did not reveal MFC activity.

Another variant of the trust game, the ultimatum game, lends itself to iterative exchanges and has been used to study trust, reciprocity and moral judgment. In the ultimatum game an investor is endowed with a sum of money and asked to pass some proportion of that money on to a trustee. In the process of the exchange the proportion of the endowment passed is multiplied by some factor. The trustee then has the choice of returning some portion of the multiplied endowment back to the investor. In one study participants were paired with fictional partners who were described as morally good, neutral or bad (Delgado, 2005) (Table 1). The authors contrasted incongruent (sharing with a morally bad person or not sharing with a morally good person) greater than congruent choices and found activation in the cingulate cortex.

King-Casas (2005) found that the investor showed middle cingulate cortex when submitting his decision and trustee showed anterior cingulate cortex when the investor's decision was revealed (Table 1). Tomlin (2006) found that switching roles, investor or trustee, had no impact on this activation. In other words, submission of a decision by either player activated middle cingulate (MCC) whereas revelation of another player's decision activated anterior cingulate cortex (ACC). The MCC and ACC activation did not vary based on subject's gender or an interpersonal context condition included in the experiment. Finally, all of the tasks discussed in this section involved a non-human control condition suggesting that the regions of interest are specific to human interactions.

Table 1. *Economic-decision making and the Medial Frontal Cortex*

Study	Task	Contrast	**BA** (x,y,z)	Signal change
McCabe (2001)	Trust Game	Human > Computer	**10** (n/a)	Human .5% ↑ Computer .2% ↓
Krueger (2007)	Trust Game	Trust > Control	**9/32** (5,39,22)	not provided
King-Casas (2005)	Ultimatum Game	Investor	**32** (0,13,37)	not provided
		Trustee	**32** (7,35,-7)	
Tomlin (2006)	Ultimatum Game	Cross-brain correlations	n/a	not provided

Delgado (2005)	Ultimatum Game	Incongruent > Congruent Choices	**32** (-4, 17, 38)	bad partner share ~.45% ↑ good partner keep ~.45% ↑

Note: Tomlin (2006) restricted his exploration to the ACC.

1.4.2.2 Theory of Mind Studies

Investigators have used a variety of experimental paradigms to understand the neural basis of theory of mind, including semantic judgments, facial judgments, and trust games. In one study participants were shown pairs of words containing descriptors and nouns (Table 2) (J. P. Mitchell, Heatherton, & Macrae, 2002). Nouns were either private names or objects (i.e., fruit or clothing) and descriptors were either appropriate for the noun or not (50-50 split). During an event-related fMRI design, participants were asked to indicate if the descriptor could ever be used to describe the noun. For the pair ‘threadbare-shirt’ the participant would respond ‘yes’, because a shirt could be threadbare. However, for the pair ‘threadbare-David’ the participant would respond ‘no’ because a person could never be meaningfully described as threadbare.

Results from 14 young adults indicated that the person > object contrast was associated with both mid and ventral MFC regions. The time series from both of these regions showed that while both people and object trials resulted in a decrease from baseline, the decrease was significantly greater in object trials. This study suggested differential neural activity for people and objects in the mid and dorsal MFC. However, the design was not able to test if the mid and dorsal MFC were due to person versus object, or due to the process of ascribing mental states to others.

Another study by the same first author employed an fMRI block-design procedure in which participants were presented with descriptor words and asked if the descriptor could appropriately be used to describe a person or a dog (Table 2) (J. P. Mitchell, M. R. Banaji, & C. N. Macrae, 2005). The descriptor words were either psychological states (e.g., curious) or names of body parts (e.g., artery). The psychological state > body part contrast revealed differences in the MFC regardless of block type (person or dog). People and dogs had similarly high parameter estimates whereas the control condition was lower. Because the dorsal MFC was activated in both the person and dog blocks, the authors concluded that the dorsal MFC does not simply represent person-hood, but is involved in ascribing mental states to other sentient beings.

Another pair of studies involved judgment of others based on faces (Table 2). In the first of these studies, participants were asked to judge how pleased the person in the picture looked to have their picture taken during an event-related fMRI design. In a control condition participants judged how symmetrical the face appeared. The psychological state > control contrast resulted in dorsal MFC. The time series from these regions showed that both psychological state and symmetry trials resulted in a decrease from baseline, but the decrease was significantly greater in symmetry judgments.

In the second study involving judgment of faces, participants were introduced to images of two individuals whom they did not know and asked to read a brief paragraph about each person (J.P. Mitchell & Banaji, 2006) (Table 2). One was described, not by name, as conservative (i.e., the conservative target) and the other as liberal (i.e., the liberal target). While in the scanner, participants were presented with a wide-range of descriptor phrases (e.g., "would drive a small car for environmental reasons" or "would enjoy going home for Thanksgiving"). Using a Likert scale, participants rated if the conservative and liberal targets would agree with the phrase. Participants also rated the extent to which they agreed with the descriptor. Participants were assessed for their own political views at the end of the study. Therefore, for each participant one of the pictured people was similar and the other was dissimilar.

The similar > dissimilar contrast revealed significant differences in ventral MFC. The time series data showed an increase in activity in similar trials, and a decrease in activity during dissimilar trials, as compared to fixation. The dissimilar > similar contrast revealed significant differences in dorsal MFC. In this area similar and dissimilar resulted in increased activity from fixation. This study also included potentially interesting individual differences findings. Namely, activity in the ventral MFC was positively correlated with the political difference score of the participant and the target (r=.54) suggesting that the ventral MFC becomes more activated by differences in others. Activity in the dorsal MFC was negatively correlated with the political difference score of the participant and the target (r=-.72) suggesting that the dorsal MFC deactivates when presented with different others. The main results were consistent with previous findings implicating the MFC in theory of mind abilities, but also suggested a meaningful functional division of the region. More ventral areas of the MFC were associated with self-referential thinking whereas dorsal areas were more related to conceptualizing other's mental states.

Table 2. *Judgments of others in the Medial Frontal Cortex*

Study	Task	Contrast	BA (x,y,z)	Signal change/ Parameter Est.
Mitchell (2002)	Semantic judgments	other > object	**9** (0,54,21) **32** (3,39,0)	Other .06% ↓ Object .3% ↓
Mitchell	Facial	other >	**9**	Other .09 % ↓

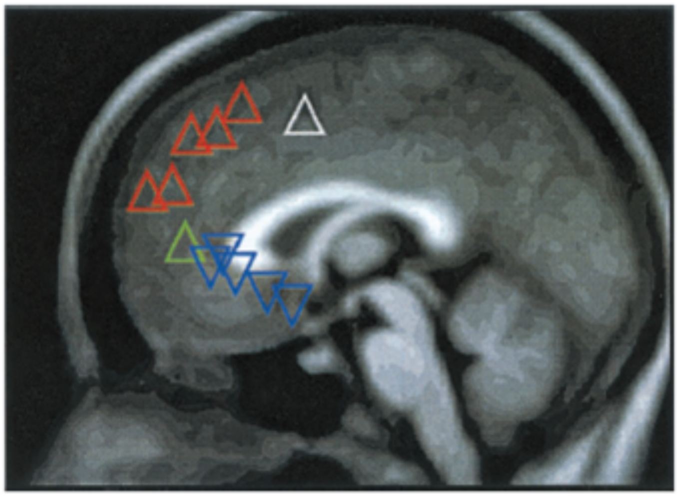
(2005)	judgments	control	(-9,51,36)	Control .19% ↓
Mitchell (2005)	Semantic judgments	other > control	**9** (9,54,36)	Other β =1.1-1.2 Control β=.5 - .9
Mitchell (2006)	Facial judgments	similar> dissimilar	**10** (17,53,7)	Similar .18% ↑ Dissimilar .11 ↓
		dissimilar> similar	**8** (-9,45,37)	Similar .57% ↑ Dissimilar .82% ↑

1.4.2.3 Self-reference Studies

In a study of self-referential material, Gusnard (2001) found that different areas of the MFC activate while other areas deactivate based on the type of judgment being made by participants (Table 3). In the block design fMRI procedure, 24 participants were presented with pictures from the International Affective Picture Set (Lang, Bradley, & Cuthbert, 1997) and asked to rate either their emotional reaction to the pictures (i.e., pleasant, unpleasant, or neutral) or the location of the pictures (i.e., inside, outside, or unsure).

The self-emotion > fixation contrast revealed increased signal change in the dorsal MFC but a decrease in signal change in the ventral MFC. The location > fixation contrast showed the same pattern of activity, but to a lesser degree. The self-emotion > location contrast showed increased activation in dorsal MFC and ventral MFC. However, the ventral section the self-emotion > location contrast only appeared as an increase in activation *relative* to the decrease in activation in the location > fixation contrast (See the green triangle in Figure 4). The authors emphasized the need for including a fixation condition and presenting task > fixation contrasts because deactivation in the ventral MFC is a relatively common finding (D.A. Gusnard & Raichle, 2001).

Figure 3. *Representation of Increases and Decreases in Activation from the MFC and Paracingulate from Gusnard (2001)*



Note: The white triangle represents the overlap of increased actitivation in the self > fix and ojects > fix contrasts. The red triangles represent areas of increased activation in the self > object contrast. The green triangle represents an area of increased activity in the self > object contrast that was a result of decreased activity during the object > fix contrast. The upside-down blue triangles represent common areas of decreased activation in the self > fix and location > fix constrast

In a semantic judgment task, Macrae et al (2004) found results consistent with Gusnard (Table 4) (2001). Participants were presented with adjectives and asked to respond 'yes' if the adjective was self-descriptive and 'no' if it was not. The task > fixation showed increased signal change in dorsal MFC and decreased signal change in ventral MFC. The self-descriptive > not self-descriptive contrast revealed differences in both dorsal and ventral MFC. In the dorsal MFC, the not-self-descriptive trials showed a greater increase in signal change from baseline than self-descriptive trials. On the other hand, both conditions showed decreased activation as compared to baseline in the ventral MFC.

This decrease was more substantial in the not-self-descriptive trials. Finally, participants' memory for the adjectives was assessed at the end of the experiment. Activation in the ventral MFC was associated with the contrast of remembered greater than forgotten words. Both conditions were associated with a decrease from baseline, although the decrease was more substantial for words that were forgotten.

Table 3. *Self-referential judgments in the Medial Frontal Cortex*

Study	Task	Contrast	**BA** (x,y,z)	Signal change
Gusnard (2001)	Image judgment (IAPS)	self > fix	**6/32** (-5,3,48)	Self ↑
			24,32,24/32, 25 Mean (-3,20,-2)	Self ↓
		location > fix	**6/32** (-3,3,48)	Location ↑
			24,32,24/32, 25 Mean (0,22,-4)	Location ↓
		self > location	**6,8,9,10** Mean (-5,38,37)	Self ↑
			32 (-3,41,8)	Self ↑ *(relative to decrease in location)*
Johnson (2002)	Semantic judgment	self > control	**32** (0,54,8)	Self ↑
Zysett (2002)	Semantic judgment	self > control	**10** (-6,55,13)	Self .13% ↑ control -.06% ↓
Macrae (2004)	Semantic judgment	task > fix	n/a	↑
			10 (n/a)	↓
		self > not self	**10** (-9,50,0)	self .09% ↓ not self .12% ↓
			32 (2,19,40)	self .22% ↑ not self .15% ↑
		self memory hits > misses	**32** (0,50,8)	hits .09% ↓ misses .18% ↓

1.4.2.4 Studies contrasting Self-referential Judgments and Theory of Mind

Investigators have used semantic judgment, image judgment, and avatar perspective-taking paradigms to study the differences in the neural basis of self-reference and theory of mind. In a semantic judgment paradigm there was a decrease from baseline in ventral MFC, but no increase from baseline in dorsal or ventral MFC (Table 4) (Kelley et al., 2002). The self > other contrast revealed differences in the ventral PFC. The time series showed that both other and control conditions were associated with a greater decrease in activity than in the self condition. Finally, the other > self contrast revealed posterior cingulate activation.

Using a paradigm similar to Gusnard, Ochsner (2004) contrasted the neural basis of self-reference and theory of mind (Table 4). While viewing IAPS pictures, participants were asked to report their emotion and the emotion of the person in the picture. The control condition involved judging the location of the picture. Both self > control and other > control contrasts were presented. The overlap of these two contrasts resulted in a left and right dorsal MFC particle. Both particles were associated with increased signal change from baseline in the self and other condition and decreased signal change in the control condition. The changes in signal were more pronounced in the right particle. The self > other contrast resulted in middle and dorsal MFC. In both regions, the time series associated with self-reference showed a greater increase in activity than the other or control conditions. The other > self contrast resulted in lateral prefrontal cortex. The time series data from this region showed a decrease in activity associated with the self-reference, but an increase in activity associated with other judgments and the control condition. In this study, when the self-referential and other conditions were directly contrasted, the self-referential activity remained medial whereas judgments of others were lateral. A similar pattern was found using avatars in a non-emotional perspective-taking task (Table 4) (David et al., 2006).

Ochsner (2005) presented two experiments both of which found that self-references activated dorsal MFC and other-references activated dorsal, middle and ventral conditions. The experimental method of this study was designed to disentangle differences between direct ("I am funny") and indirect ("Tommy thinks I am funny") self-knowledge, not to contrast self and other (Table 4). In the final study, the self > control and other > control contrasts both revealed differences in the ventral MFC but signal change was not provided (Schmitz, Kawahara-Baccus, & Johnson, 2004) (Table 4). The self > other contrast resulted in no findings in the MFC.

Table 4. *Contrasts of Others versus Self-referential Judgments in the Medial Frontal Cortex*

Study	Task	Contrast	BA (x,y,z)	Signal change
Kelley (2002)	Semantic judgment	task > fix	null n/a	null ↓
		self + other > control	**6** (0,14,42)	↑
		self > other	**10** (10,52,2)	self .1% ↓ other .3% ↓ case .3% ↓
Schmitz (2004)	Semantic judgment	self > control	**10** (6,56,4)	n/a
		other > control	**10** (-4,58,4)	n/a
		self > other	null	null
Ochsner (2004)	Image judgment (IAPS)	self > control & other > control (overlap)	**9** (-4,52,42)	self.06% ↑ other .07% ↑ control .23% ↓
			9 (2,56,40)	self.25% ↑ other .2% ↑ control .39% ↓
		self > other	**9** (-2, 58, 38)	self .25% ↑ other .01% ↓ control .06% ↓
			9 (-2, 50,16)	self .45% ↑ other .01% ↑ control .4% ↓
		other > self	**44** (-56,6,18)	self .05% ↓ other .03% ↑ control .02% ↑
Ochsner (2005)	Exp.1 Semantic judgment	self > control	**24/32** (6,32,30)	n/a
		other > control	**24/32** (-8,40,34)	n/a
			32/19 (-2,56,20)	n/a
			32/10 (-2,56,4)	n/a
	Exp.2 Semantic judgment	self > control	**8** (-12,40,42)	n/a
			24 (8,32,32)	n/a
David (2006)	Perspective taking using avatars	self > other	**10** (-2,39,-8)	n/a
		other > self	**44** (-43,8,32)	n/a

1.5. Conclusions and Future Directions

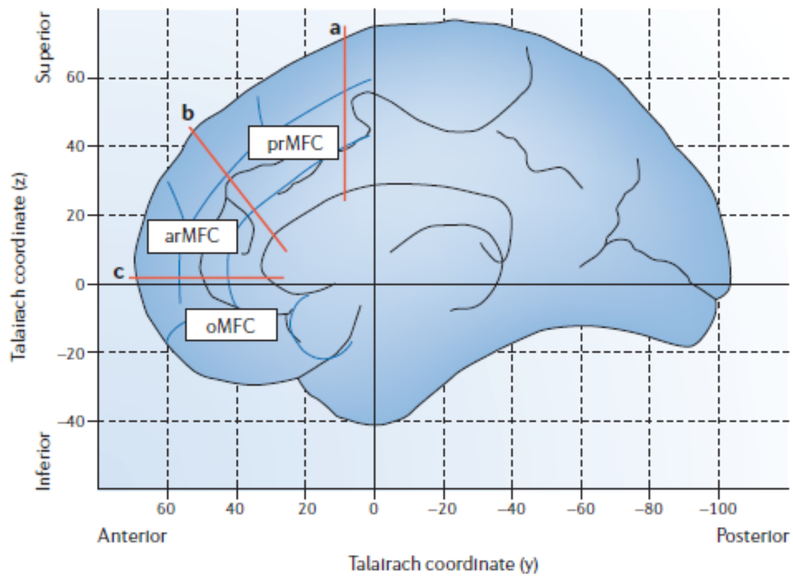
In summary, the heterogonous symptom presentation of schizophrenia has led investigators to study individual symptom dimensions. The use of a translational method to identify cognitive mechanism as endophenotypes of schizophrenia has increased the field's understanding of schizophrenia's neurobiological underpinnings (MacDonald & Schulz, 2009). Persecutory ideation has the potential to serve as an ideal prototype for developing a translational model of positive symptoms in schizophrenia for several reasons. First, persecution is a clinically significant phenomenon because of its impact on treatment adherence, violence, and suicide (Arseneault, et al., 2000; Owen, et al., 1996). Second, persecutory delusions are unlikely to be a culturally bound symptom because they are a common type of delusion across developing and developed nations (T Stompe, et al., 1993). Finally, persecution shares its self-referential nature with other type of delusion including delusions of reference and grandeur (Butcher, 2000). As a result, findings regarding persecution may be readily applicable to other types of delusional thinking.

Trust games have been used in behavioral economics and psychology to understand individual (Eckel & Wilson, 2004; Paulus, et al., 2003) and group differences (B. King-Casas et al., 2008; McCabe, et al., 2001) in personality traits related to cynicism. However, until recently trust games have not been able to capture the self-referential nature of persecution. The Minnesota Trust Game is a variant of a trust game that contains conditions designed to selectively measure aversion to risk, rational mistrust, and suspiciousness. The suspiciousness condition has reliably showed a specific relationship to the Alienation subscale of MPQ, a personality trait that has been related to persecution in schizophrenia (DiLalla & Gottesman, 1995; M.K. Johnson, Rustichini, et al., 2009). The results from the Minnesota Trust Game indicate that it is ideally parameterized to study persecution independent of related constructs.

Since the original, the Minnesota Trust Game has undergone four iterations of data collection and task modifications. In each iteration the relationship between the Supciousness condition and a measure of persecuted personality has been established. As a result, the MTG has been adequately tested for translation into new levels of inquiry. Translating the MTG into a schizophrenia sample requires modifications of the task in order to enable patient comprehension while maintaining the tasks' construct validity. The modifications made to the task are discussed to some extent in Chapter 3 of this manuscript as well as Appendix 3.

In their review of social cognition in the medial frontal cortex (MFC), Amodio and Frith (2006) suggest that the MFC can be divided into three functionally unique regions, the orbital (oMFC), anterior rostral (arMFC), and posterior rostral (prMFC) MFC (Figure 4). The findings from the current review are consistent with Amodio and Frith's (2006) argument that social judgments, including theory of mind and self-referential thinking, are often associated with the arMFC. However, the neurobiological differences between theory of mind and self-referential thinking remain inconclusive.

Figure 4. *Functional regions in the MFC suggested by Amodio and Frith (2006).*



Studies using economic decision-making tasks identified multiple regions though parts of the cingulate cortex were most common. Studies using theory of mind paradigms suggest that the anterior rostral MFC (arMFC) is specific to person-person interactions. Two studies by Mitchell (2002, 2005) suggest that activity in both the dorsal and ventral arMFC is decreased under task demands, but that this decrease is lesser for mentalizing skills. Mentalizing about similar others was associated with ventral arMFC in contrast mentalizing about dissimilar others was associated with the prMFC. The authors suggest that the results support the ventral MFC as a location of simulation, a hypothetical process by which we understand another's mind based our first-person experience[1].

Regions implicated by the studies of self-referential processing in this review included the orbital MFC in addition to the anterior and posterior rostral MFC. Interpreting results in the ventral areas of the MFC necessitates close attention to neuroimaging methodology. For example, Gusnard (2001) found that the more ventral particle in the self > control condition contrast did not truly represent an increase in activity associated with self-referential thinking. In fact, the increase was a result of decreased activation during the control > baseline fixation contrast. Decreases in activation in the MFC, particularly more ventral areas, have been a relatively common finding that may be a result of the region's high metabolic rate at rest (D.A. Gusnard & Raichle, 2001). Two studies reviewed in this manuscript showed that the ventral arMFC was selectively activated during the self > control contrasts (S. C. Johnson, et al., 2002; Zysset, et al., 2002). However, these studies did not present baseline fixation contrasts.

One other study presented a task > baseline fixation contrast (Macrae, et al., 2004). In this study the task > fixation contrast showed decreased activity in the ventral but not dorsal MFC. In this same study, the self > control contrast resulted in decreased activity in the oMFC/arMFC. The control condition revealed a more substantial decrease. This parallels the signal change patterns found in theory of mind studies and supports the hypothesis that both types of social judgment are associated with

---

[1] To be clear, Mitchell et al (2006) conclude that their interpretation is weakened by the fact that being similar and being liked are frequently confounded.

deactivation in the arMFC. The decreased activation in the MFC during social cognition tasks has been used as evidence that this region is tonically engaged in self-referential and/or social-cognitive stream of consciousness.

Ochsner points (2004) out that decreased activity from baseline in a region associated with social judgment is not adequate evidence to reach this conclusion. The resting states are by their nature unconstrained and therefore difficult to interpret. However, Amodio and Frith (2006) reference a study in which the investigators confirmed that self-referential thoughts did occur during rest (D'Argembeau et al., 2005). The extent to which participants were having self-referential thoughts correlated with the MFC activity in the study. However, more research in needed to determine the relationship between the MFC and self-referential thinking.

The final section of the neurobiology section reviewed studies that included both judgments of others and self-referential conditions. Of the four studies that included direct contrasts of self > other, three of them found arMFC ranging from ventral to dorsal. Only one of the studies reviewed in this section included a contrast of task activity to baseline fixation (Kelley, et al., 2002). This study found that in the self > other contrast self-referential activity was associated with less decreased activation than judgment of others. Of the three studies that included other > self, one found ventral arMFC and two found BA 44. One interpretation of the latter two findings is that representation of the self is a basic, tonic process located in the arMFC, whereas the judgment of others is a more semantic process that requires recruitment of other brain regions.

The current review discussed the role of the amygdala in perceiving threat. Research suggests that MFC is targeted by dopamine neurons originating in the ventral tegmental area (VTA) during fear conditioning (Pezze & Feldon, 2004). Interestingly, a study that implicated the anterior rostral MFC in the decision trust, also found those with low trust/reciprocity scores had increased activity in the VTA as compared to more cooperative participants (Krueger, et al., 2007). One future direction for studying the role of the MFC in persecution might be investigating the relationship between the MFC and dopamine as means of understanding the neurobiological basis of heightened anticipation of threat (Bentall, et al., 2009). The aberrant dopamine hypothesis suggests that striatal dopamine dysregulation may cause patients with schziophrenia with positive symptoms to ascribe salience to otherwise neutral experiences or objects (Howes & Kapur, 2009). A specific finding involving dopamine, the MFC, and persecution may help to refine that hypothesis. Finally, a complete picture of the neurobiology of persecutory ideation involving the MFC and dopamine may also inform other neurological, psychiatric and developmental disorders in which persecutory ideation is present including Parkinson's, Alzheimer's diseases, Borderline Personality Disorder and Autism.

Chapter 2

Specific Aims and Hypotheses

Persecutory ideation is a common and clinically significant delusion in schizophrenia that has the potential to serve as a prototypical model for studying the dimension of positive symptoms. As a result, the current line of research was focused on developing a cognitive model of persecutory ideation with the potential for translation into neuroimaging, genetic, and treatment levels of inquiry. The Minnesota Trust Game

(MTG) is an economic decision-making paradigm that has been parameterized to successfully elicit a type of decision-making bias that is uniquely related to persecutory ideation. The current study is funded to investigate the neural basis of persecutory delusions in patients with schizophrenia, using patients without this delusion as the controls for patients with this delusion.

2.1 Specific Aims

1) Consistent with a translational approach, the Minnesota Trust Game (MTG) has been studied extensively in individuals without psychiatric disabilities. This study will evaluate the relationship between persecutory delusions and decision-making processes associated with trust in schizophrenia.
2) The review of the neurobiology of trust within the social cognition literature in Chapter 1 and previous research using the MTG have identified the medial prefrontal cortex, paracingulate, anterior cingulate, amygdala, insula, and orbital frontal cortex as key regions in trust. This research will use a mask restricted to these regions to identify neural activity associated with the Suspiciousness, Rational Mistrust and Risk Aversion conditions of the MTG in people with schizophrenia.
3) Finally, this study will investigate the relationship between neural activity identified in Specific Aim 2 and a symptom measure of persecutory ideation.

2.2 Decision-making and Symptom Hypotheses

The Minnesota Trust Game provides the opportunity to assess the neural basis of conceptualizing other's intentions under different emotional conditions. When the *temptation* is high for the Other Player, the participant is deciding to trust another person who has an incentive to betray. However, when the *temptation* is low the participant is deciding to trust a person who has no incentive to betray. The relevant behavioral effects have been established in control participants as a *decision-agent*temptation*adverse payoff* interaction from a repeated measures logistic regression. The key finding in this interaction is that the *temptation* differentiates behavior when the *decision-agent* is the other player. This finding has been replicated in 2 samples of undergraduate students (n=73 and n=251) and a sample of monozygotic twins (n=23 pairs). The twins serve as the best comparison sample for patients as they were recruited from the general population as opposed to a college campus. In the sample of twins, participants were significantly less likely to trust another player when that person had financial incentive to betray (OR = .38). Additionally, participants were more sensitive to financial risk when asked to take a chance (OR = .39) as opposed to trusting another person (OR = .61). We predict that patients with schizophrenia will show a similar pattern of results as manifested by the interaction of *decision-agent*temptation*adverse payoff*. We will test for the interaction using the same methods used in controls, a repeated measures logistic regression. As we did with the control samples, we will test for the directionality of effects by calculating odd ratios.

Another critical finding in the Minnesota Trust Game (MTG) has been the relationship between measures of persecuted personality and deciding to trust another person who has no financial incentive to betray. In the same sample of twins (n=23 pairs), participants with a T-score greater than 60 on the Alienation scale from the Multidimensional Personality Questionnaire (Patrick, et al., 2002; Tellegen & Waller, 2008) were significantly less likely to trust another player who had no financial incentive to betray (OR=.238, 95% CI [.101, .567]. To measure individual differences in persecution we will use the Suspiciousness item from the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962). In order avoid confusion between the Suspiciousness item on the BPRS and the Suspiciousness condition in the MTG, we will refer to the Suspiciousness item from the BPRS as 'Persecutory Ideation'.

We predict that patients with schizophrenia will show a similar patter of results as manifested by the 4-way interaction of *decision-agent* by *temptation* by *adverse payoff* by *Persecutory Ideation*. We will test for this finding using the same methods used in past studies, a repeated measures logistic regression. We will test for the directionality of effects by calculating odd ratios. Specifically, we anticipate that higher scores on Persecutory Ideation will be associated with less trusting behavior in the presence of financial risk when the Other Player has no incentive to betray.

2.3 Neuroimaging Hypotheses

2.3.1 Decision-making Activation

Review of the neurobiology of trust within the social cognition literature as well as findings from a previous study of the Minnesota Trust Game (MTG) suggest that the medial prefrontal cortex, paracingulate, orbital frontal cortex, anterior cingulate, insula and amygdala are regions of interest for the current study. In order to understand the effect of the MTG task manipulations on neural activity in patients with varying degrees of Persecutory Ideation, we will model our neuroimaging contrasts after the findings in the behavioral data. All significant regions of interests will be explored to determine the directionality of effects (i.e., activation vs. deactivation).

2.3.1.1 Ventromedial Prefrontal Cortex

Tasks designed to measure conceptualizations of the self and others have identified the ventromedial prefrontal cortex (vmPFC) (Amodio & Frith, 2006). Some research has shown that more ventral areas in the vmPFC were associated with self-referential thought processes (Debra A. Gusnard, et al., 2001) while more dorsal areas are associated with judgments of others (J.P. Mitchell & Banaji, 2006). This pattern has not been found in every study (Ochsner, et al., 2004). Also of note, more vmPFC is part of the brain's default mode network (DMN). The DMN's high metabolic resting state increases the likelihood of task-related deactivations in this region. This can lead to misleading findings and necessitates the presentation of task vs. fixation contrasts in order to clarify the directionality of effects (Debra A. Gusnard, et al., 2001).

Since decision-making paradigms like the MTG require participants to model both their own intentions and the intentions of others, the vmPFC is a primary region of interest. In a sample of 46 monozygotic twins without schizophrenia, the vmPFC was associated with the Suspiciousness greater than Rational Mistrust contrast (Figure 5) (MacDonald, Porter, Johnson, & Krueger, 2008). Finally, the vmPFC is also a region of interest because of findings of reduced vmPFC activation in patients with persecutory delusions compared to patients without persecutory delusions and controls (Pinkham, Hopfinger, Ruparel, et al., 2008; Williams et al., 2004b; Williams, et al., 2007).

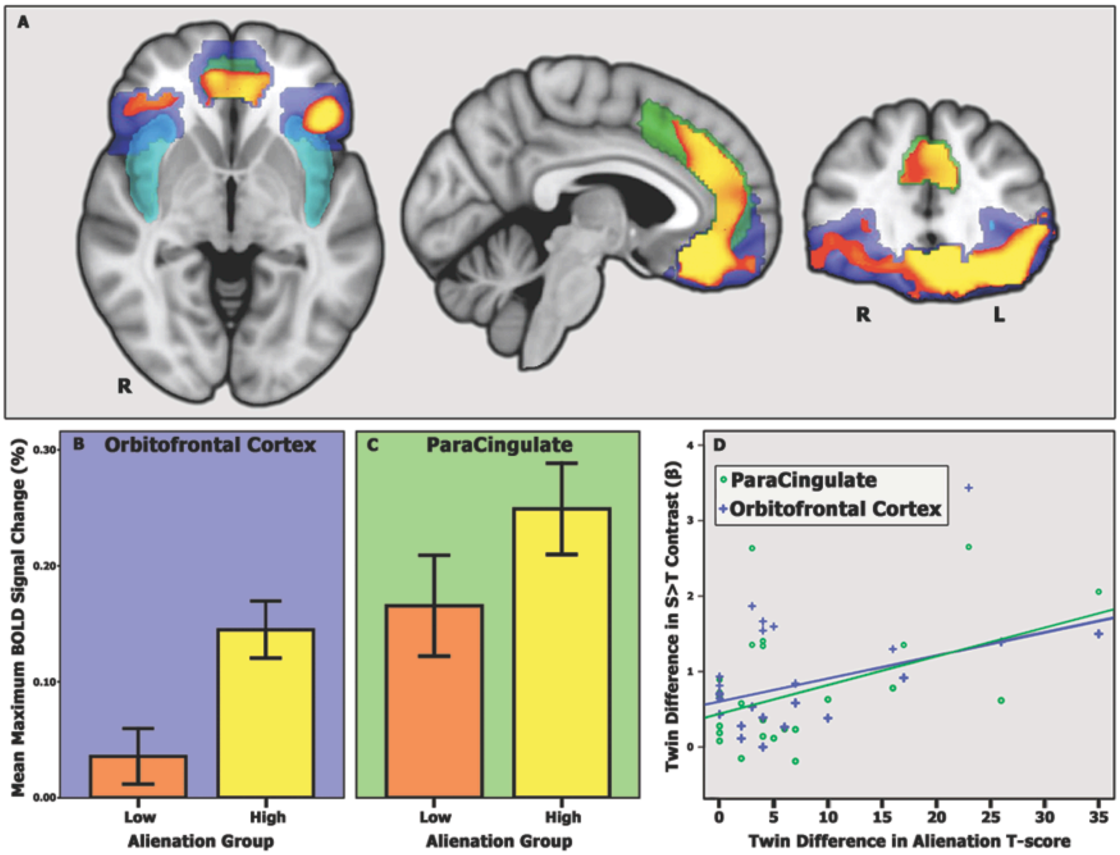
We predict that the vmPFC will show changes in activation in the Other Player but not the Risk Aversion conditions since more mentalizing is needed in the former. Additionally, we predict that we will find vmPFC in the Suspiciousness greater than

Rational Mistrust contrast because of the Suspiciousness condition's proposed relationship with Persecutory Ideation. Since one of the defining features of persecutory delusions is self-referential thinking, we predict that changes in activation in vmPFC will be associated with individual differences in Persecutory Ideation.

2.3.1.2 Paracingulate Cortex

Activation in paracingulate cortex (PcC) has also been associated with judgments of other's mental states using both theory of mind (Ochsner, et al., 2005) and economic decision-making paradigms (Krueger, et al., 2007). A functional neuroimaging study of the Minnesota Trust Game in a sample of monozygotic twins without schizophrenia found PcC activation in a contrast of the Suspiciousness greater than Rational Mistrust conditions (Figure 5) (MacDonald, et al., 2008). Additionally, activation in the PcC reflected environmentally mediated influences on brain activity related to persecuted personality. The authors interpret this activation as reflecting the additional processing required to conceptualize the intentions of someone with no financial motivation to betray as opposed to the more automatic conceptualization of the other player in the Rational Mistrust condition. Based on these findings the PcC is a primary region of interest where we expect to see activation during the Suspiciousness condition and a relationship between activation and Persecutory Ideation.

Figure 5. *Activation and Individual Differences Associated with Behavior and Neural Activity from the Minnesota Trust Game in a Sample of Twins (n=46).*



Note: Figure 5 depicts results from the study of 46 monozygotic twins using the Minnesota Trust Game (MacDonald, et al., 2008). Activation in the paracingulate, orbital frontal cortex and anterior insula were found when contrasting the Suspiciousness greater than Rational Mistrust conditions. The difference in twin pair's Alienation T-scores was positively correlated with the difference between their parameter estimates in the orbital frontal cortex and paracingulate.

2.3.1.3 Orbital Frontal Cortex

The orbital frontal cortex (OFC) is associated with assessing potential rewards and losses as well as guiding decision-making behavior. In our sample of monozygotic twins without schizophrenia, lateral OFC activation was found in a contrast of the

Suspiciousness greater than Rational Mistrust conditions (Figure 5) (MacDonald, et al., 2008). Similar to the PcC, activation in the lateral OFC reflected environmentally mediated influences on brain activity related to persecuted personality.

In a guessing paradigm, lateral posterior OFC was associated with unstable circumstances (i.e., participant's cumulated reward was rising or falling quickly via task manipulation) (Elliott, Dolan, & Frith, 2000). The authors conclude that at this point in the task participants felt as though their "luck was about to change" and felt compelled to override previous response selection in order to try a new strategy. The increased activation in the lateral OFC in the Suspiciousness condition may reflect a change in strategy from the Rational Mistrust condition during which not-trusting in financial risk circumstances is more prudent. Based on our previous research in twins and the literature, the OFC is a primary region of interest for this study. We predict that patients, like the twins, will activate lateral OFC in the Suspiciousness condition and show a relationship between OFC and Persecutory Ideation.

2.3.1.4 Anterior Cingulate Cortex

The anterior cingulate cortex (ACC) has been associated with a wide range of cognitive abilities including attention and monitoring of conflict and error probability (MacDonald, Cohen, Stenger, & Carter, 2000). The review of the economic decision-making literature in Chapter 1 suggested that the ACC might be spatially and functionally divided into "me" and "not me" regions (B. King-Casas, Tomlin, D., Anen, C., Camerer, C.F., Quartz, S.R., Montague, R.P. , 2005; Tomlin, et al., 2006). Such a distinction may be related to the self-referential themes found in persecutory ideation. Since this activation in previous research has been found in circumstances with a human and not other agents, we would predict that this activation would manifest in a contrast of the Other Player greater than Risk Aversion.

2.3.1.5 Insular Cortex

Within the field of neuroeconomics, the anterior insula is known for its relationship to judgments of unfair offers in the Ultimatum Game (Delgado, 2005; A. G. Sanfey, et al., 2003). Perhaps more relevant to the current study are findings that the insula is sensitive to the anticipation of risk. Paulus (2003) found anterior right insula activation was associated with risky decisions and that right inferior frontal gyrus/insula and posterior left insula were associated with risky decisions when controlling for risky choices that were "punished" (i.e. involved monetary loss for the participant). Of note, the outcome of participants' choices in the Paulus (2003) study was determined by a computer whereas the Delgado (2005) and Sanfey (2003) study found that anterior insula activation was unique to human interactions. One implication from these findings is that insula activation involving judgment is specific to human interaction (e.g., moral judgment) but insula activation related to risk-taking is non-specific. The parallel human and non-human conditions of the MTG provide an opportunity to test this hypothesis.

2.3.1.6 Amygdala

The role of the amygdala in trust is complex. The amygdala has been associated with appraisal of threat (R. Adolphs, 2001; R. Adolphs, Tranel, D., & Damasio, A.R., 1998; Winston, et al., 2002). However, the amygdala's relationship to oxytocin speaks to its role in trusting behaviors (Kosfeld, et al., 2005). Decreased amygdala activation has been indentified in studies of social cognition and persecution in schizophrenia (Pinkham, Hopfinger, Pelfrey, Piven, & Penn, 2008; Pinkham, Hopfinger, Ruparel, et al., 2008; Williams, et al., 2004b; Williams, et al., 2007). Pinkham (2008) suggested that the reduced amygdala activation in persecuted patients may reflect a deficit in the ability to link social stimuli with emotional value. If the amygdala is associated with the appraisal of threat we would predict amygdala activation in the Rational Mistrust condition. Finally, if persecuted individuals are impaired in their ability to link social stimuli with thier emotional value, then we would anticipate that higher persecution scores would be associated with less amygdala activation.

Chapter 3

Method

3.1 Participants

Thirty-eight individuals with schizophrenia or schizoaffective disorder between the ages 18 and 45 participated in the study. Participants were excluded based on MRI scanning contraindications, history of head injury or prolonged unconsciousness, or substance and/or alcohol abuse or dependence within the past 6 months. Participants with an IQ less than 75 as measured by the Wechsler Test of Adult Reading (2001) were excluded. Of the 38 participants, 32 were included in the final analysis. Though efforts were made to only recruit eligible participants into the protocol, six participants were lost after enrollment. Two participants were unable to complete the data collection because their size made the scanner uncomfortable, one participant was unable to stay awake consistently during the scan, one person's vision was too poor to be corrected by the set of MR safe glasses and two people complained of claustrophobia. All participants completed an informed consent process. As part of this process, the experimenter explained that that the study would take 4 hours and that the compensation was $80 plus an amount between $10 and $45 depending on their choices during the experiment. The experimenter explained that it was not possible for the participant to earn less than $90. The average amount of total compensation was $110.

3.2 Psychiatric Diagnoses and Symptom Ratings

The study used the Mood and Psychosis Modules of the SCID-I/P for the DSM-IV-TR (First, Spitzer, Gibbon, & Williams, 2002) to determine the presence of schizophrenia or schizoaffective disorder. The presence of past 6 month substance abuse or dependence was assessed using the J and K modules from the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Psychiatric symptoms were assessed using the Brief Psychiatric Rating Scale - Expanded Version (BPRS) (Lukoff, Nuechterlien, & Ventura, 1986; Overall & Gorham, 1962). The Suspiciousness item from the BPRS was used as a measure of individual differences in persecuted beliefs. In order to avoid confusion between the Minnesota Trust Game Suspiciousness condition and the BPRS Suspiciousness item, we will refer to the BPRS Suspiciousness item as 'Persecutory Ideation'.

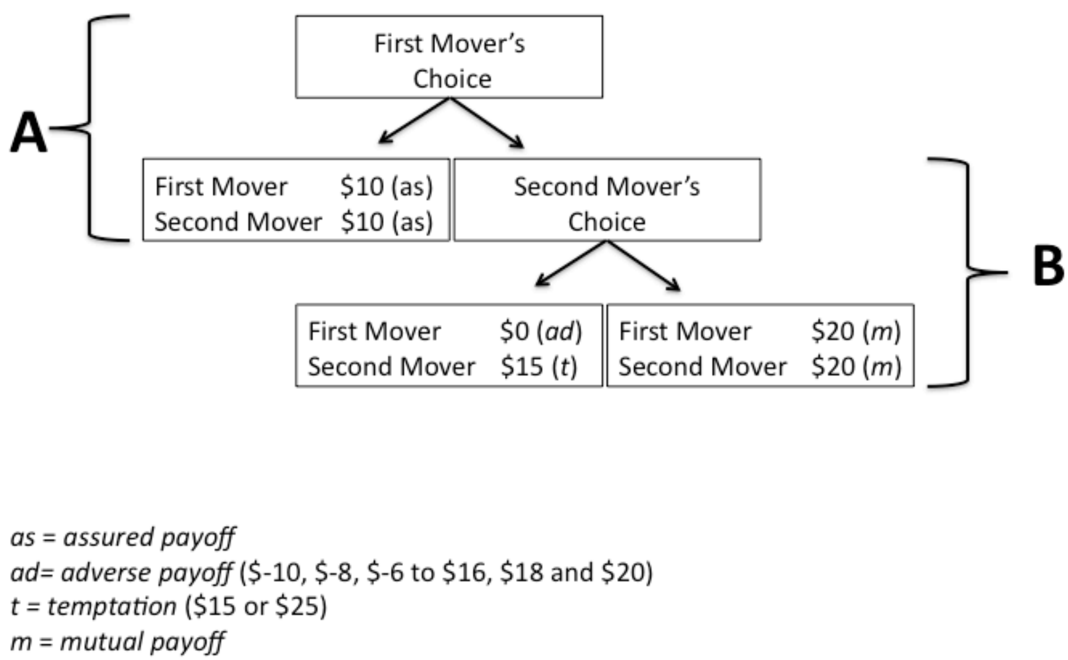
This author and the assistant lab director, Dr. Dori Henderson, administered the SCID modules and the BPRS. We met with Dr. Scott Sponheim for diagnostic supervision and participated in BPRS reliability rating rounds as part of a larger multi-site study (CNTRACS). The intraclass correlation coefficient for BPRS Persecutory Ideation item only for CNTRACS raters was .91. Directly comparing Dr. Henderson and the current author alone on this item, the ICC was .84 calculated from 5 patients.

3.3 Experimental Design and Behavioral Analyses

3.3.1 Minnesota Trust Game Design

The Minnesota Trust Game (MTG) was used to measure decision-making biases (Figure 6). This version of the MTG was designed to facilitate comprehension in this sample while maintaing the overall task design (Appendix 3). Each trial of the MTG included two constants and three variables for the participant to consider. The constants were the *assured payoff* (*as*), which was always equal to $10, and the *mutual payoff* (*m*), which was always equal to $20. The variables were the *decision-agent* (*da*), which was the Other Player or the Coin Flip, the *adverse payoff* (*ad*), which ranged from $-10 to $20, and the *temptation* (*t*), which was either $15 or $25.

Figure 6. *Minnesota Trust Game Example Decision-tree*



Note: A. Decision-tree for a First Mover Suspiciousness trial. B. Decision-tree for a Second Mover Spitefulness trial.

3.3.1.1 First Mover Game Design

The MTG included four conditions: Rational Mistrust, Suspiciousness, Risk Aversion 25 and Risk Aversion 15. These four conditions were collectively referred to as the 'First Mover' game (Figure 1A). During the Rational Mistrust condition the *decision-agent* was the Other Player and the *temptation* was equal to $25. Both conditions involved the First Mover choosing between the *assured payoff* and allowing an anonymous player to determine their winnings. The Risk Aversion $25 and $15 conditions paralleled the Rational Mistrust and Suspiciousness conditions except that *decision-agent* was a Coin Flip instead of the Other Player.

3.3.1.2 Second Mover Game Design

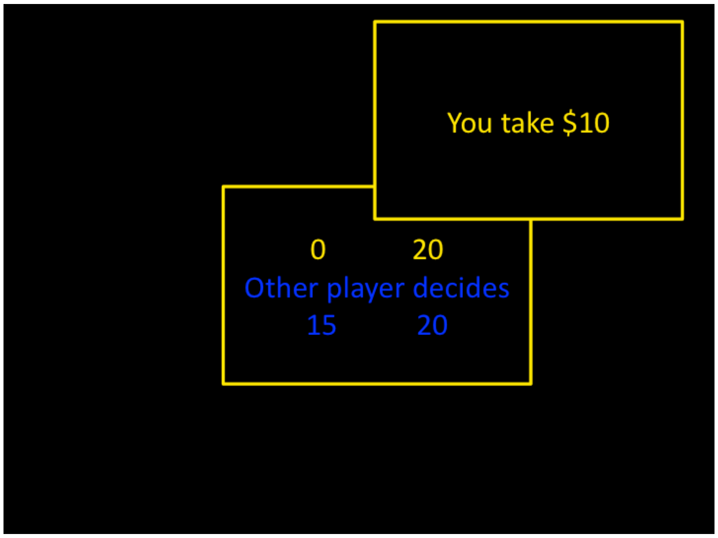
The MTG included two additional conditions: Selfishness and Spitefulness. These two conditions were collectively referred to as the 'Second Mover' game (Figure 1B). During the Selfishness condition the *temptation* was equal to $25. During the Spitefulness condition the *temptation* was equal to $15. Both conditions involved the Second Mover choosing between the *temptation* and the *mutual payoff* (*m*). If the Second Mover chose the *temptation* then the First Mover received *adverse payoff*. If the Second Mover chose the *mutual reward* then both players received $20.

3.3.1.3 *Stimuli Presentation and Responses*

Each trial consisted of a black screen depicting two rectangular "cards" (Figure 2). To select the top card participants pressed the button that physically corresponded to 'top' on the response device. To select the bottom card, participants pressed the button that physically corresponded to 'bottom' on the response device. Participants had a 6 second response window. The location of the top card was counterbalanced such that it was in the right portion of the screen for half of the participants and in the left portion for the remaining half.

For each trial of the First Mover game participants were presented with 2 “cards” depicted on a black screen (Figure 7). To facilitate comprehension, the First Mover’s winnings were presented in yellow and the Second Mover’s in blue (Figure 7). The top card represented the *assured payoff*. The bottom card was conditional on the Second Mover’s choice. If the Second Mover chose $15 (*temptation*) then the First Mover received $0 (*adverse payoff*). If the Second Mover chose $20 (*mutual reward*) then the First Mover received $20. The coin trials were identical except that “Coin Flip” was printed in the middle of the bottom card. In the Second Mover game “You take $20” was printed on the top card the numbers representing the *temptation* and the *adverse payoff* were printed in a centered column on the bottom card. To minimize eye movement the bottom card was displayed at the center fixation point.

Figure 7. *Minnesota Trust Game Visual Presentation*



Note: In this figure the *temptation* = $15 and the *adverse payoff* = $0. As in all trials, the *mutual reward* = $20 and the *assured payoff* = $10.

3.3.1.4 *Protocol Chronology and Training*

After the informed consent process participants were trained on the Second Mover game. As part of the training for the Second Mover game the experimenter explained the following:

> *The decisions you make during this game will affect the amount of money you will win today. The decisions you make in this game may also affect the amount of money another future study participant will win. You should make your decisions based on what you think is best. There is no right or wrong answer. At the end of the day I will randomly select one of your choices to add to your payment.*

Participants then completed the Second Mover task before beginning training for the First Mover game. As part of the training for the First Mover game when the decision-agent was the Other Player the experimenter explained the following:

> *The decisions you make during this next game will also affect the amount of money you will win today. Also, the choices of another study participant may affect your winnings. This other study participant made choices just like the ones you just made. Now, you need to decide whether or not you want to trust this other person to determine your winnings. You should make your decisions based on what you think is best. There is no right or wrong answer. At the end of the day I will randomly select one of your choices to add to your payment.*

Immediately after completing the training for the First Mover Other Player game, the participant was trained on the First Mover Risk Aversion conditions. As part of the training for the First Mover Risk Aversion conditions game the experimenter explained the following:

> *This next game is a little bit different. Instead of another participant determining the winnings, it's a coin-flip. So, you need to decide if you want to let a coin flip determine your winnings. You should make your decisions based on what you think is best. There is no right or wrong answer.*

After completing the training for First Mover task the participant completed 108 choices as the First Mover during a series of functional neuroimaging scans.

3.4 Analysis

3.4.1. Decision-making Analyses: First Mover

All analyses involving the decision-making were done using logistic regression in STATA (StataCorp. 2005. *Stata Statistical Software: Release 9*. College Station, TX: StataCorp LP.) Regression coefficients from significant effects were translated into odds ratios for interpretation. The dependent variable for the First Mover analyses was choice. Taking the *assured payoff* was coded at '0' and taking a chance with the Other Player or Coin was coded as '1'. *Decision-agent*, *temptation*, *adverse payoff* and relevant interaction terms were entered as predictors. Task comprehension was operationalized as a three-way interaction of *decision-agent*temptation*adverse payoff*. Participants were expected to be more trusting when the *temptation* for the Other Player to betray is low than when the *temptation* was high. This effect was not predicted for the Risk Aversion conditions. The differential impact of the *temptation* in the Other Player conditions was predicted to become pronounced as financial risk increases, as indicated by decreased dollar values in the *adverse payoff*.

3.4.2 Decision-making and Persecutory Ideation Analyses

The Brief Psychiatric Rating Scale (BPRS) Persecutory Ideation item was added as a predictor to the Minnesota Trust Game (MTG) First Mover game analysis after the basic decision-making effects were established. We predicted that Persecutory Ideation would predict less trusting behavior in the MTG Suspiciousness condition. Furthermore, we predicted that this effect would become more pronounced as the dollar value of the *adverse payoff* decreased. Finally, we hypothesized that this relationship would not exist with any other condition of the MTG. This was operationalized as a 4-way interaction of *Persecutory*decision-agent*temptation*adverse payoff*.

3.5 Neuroimaging Data Acquisition and Preprocessing

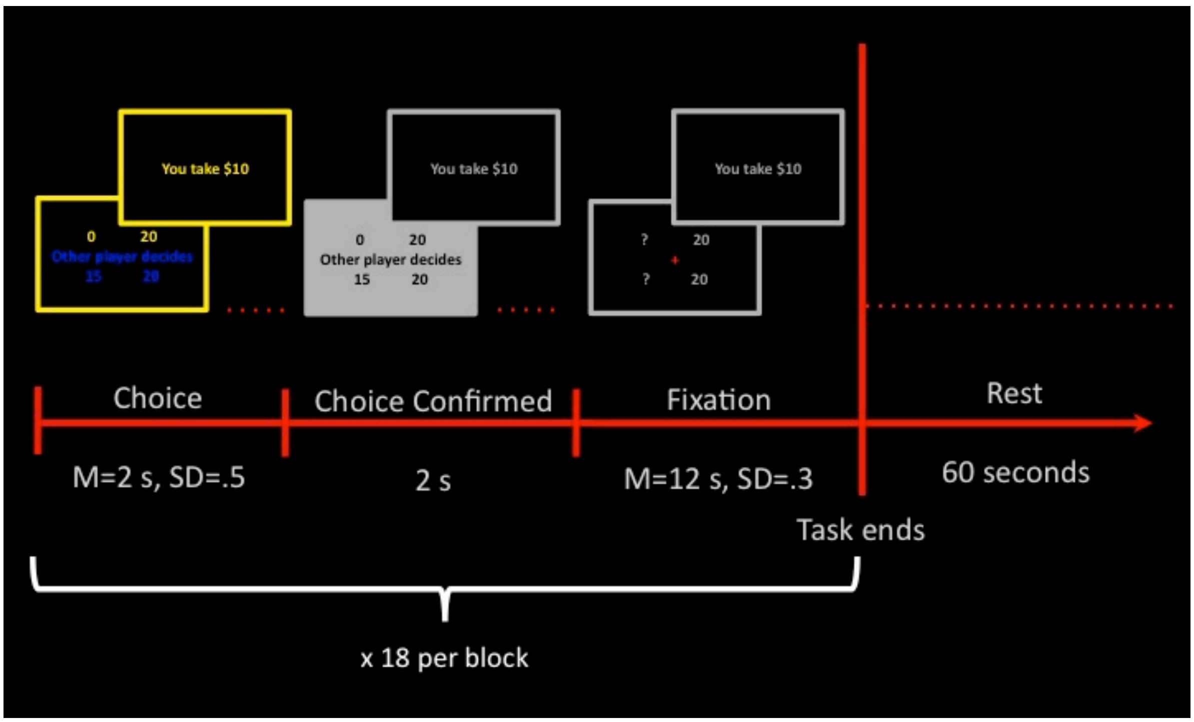
3.5.1 Imaging Acquisition

Neuroimaging data were collected using the 3T Siemens Trio MRI scanner and 12-channel head coil at the Center for Magnetic Resonance Research at the University of Minnesota. Standard task projection and response collection methods were used. Functional images were collected using an echo-planar imaging (EPI) functional sequence that maximized signal-to-noise in all regions of the brain (35 slices; plane=axial; TE=28 ms; TR=2000 ms; flip angle=90; slice thickness=3.5mm; base resolution=64; FOV=256). Structural data were collected using a whole brain magnetization-prepared rapid gradient-echo (MP-RAGE) (224 slices; plane=coronal; TE=3.65 ms; TR=2350 ms; flip angle=7; slice thickness=1mm; base resolution=256; FOV=256). Images were collected with a 12-channel head coil system. The study employed an event-related design to maximize the interpretability of activations.

Each participant completed 6 5-minute and 52-second blocks of the Minnesota Trust Game (MTG) during the scanning session (Figure 8). Half of the blocks contained only coin trials and the other half contained only Other Player trials. In order to reduce possible confusion associated with task switching, block presentation did not alternate between the Other Player and Risk Aversion conditions. The blocks were counterbalanced such that half of the participants completed all of the Risk Aversion blocks first. Each block contained 18 trials, 9 trials when t=\$15 and 9 trials when t=\$25.

Each block sampled 9 levels of financial risk associated with the *adverse payoff*. Each block contained 2 no risk (*ad*>$9) and 7 risk trials ($10>*ad*>-$10). No dollar value of the *adverse payoff* was repeated within condition. All levels of *da*, *t* and *ad* were fully crossed resulting in a factorial design.

Figure 8. *Design of Minnesota Trust Game First Mover fMRI Task*



Each trial lasted 18 seconds and was composed of 3 parts, the participant's choice, the choice confirmation and fixation. Each trial began with the choice between the top and bottom cards. The choice response window was 6 seconds. As soon as participants made a choice, the screen turned to grey to confirm that the computer registered the response. The duration of the fixation varied based on the participant's reaction time on that trial. The mean fixation period was 12 seconds. After 18 trials, the block ended with a 60 second rest period.

3.5.2 Functional Neuroimaging Data Preprocessing

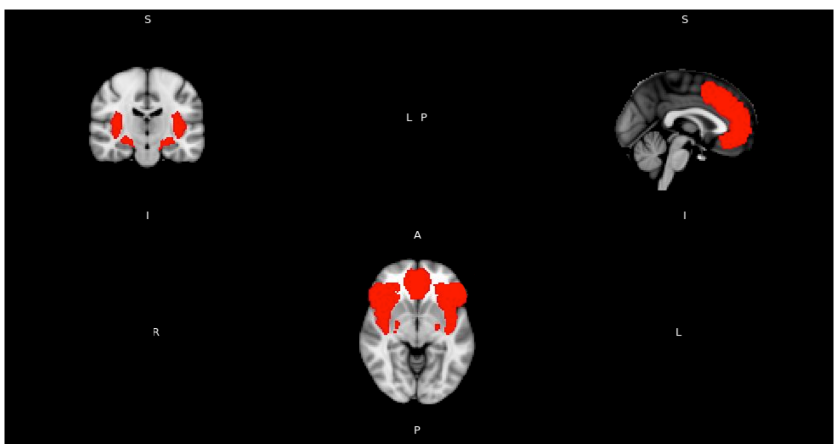
Image preprocessing followed established guidelines using FSL (Stephen M. Smith et al., 2004) for functional data and structural data. Within scan motion correction was performed by the Seimen's motion correction program (Thesen, Heid, Mueller, & Schad, 2000). FSL's slice time correction program implemented a Fourier-space time-series phase-shifting to temporally re-sample the data so that each volume in the resulting dataset approximates an instantaneous snapshot. This corrected for the fact that each slice within each volume was actually acquired at a slightly different times. Non-brain tissue removal was performed using the FSL Brain Extraction Tool (BET) (S. M. Smith, 2002). Spatial smoothing was performed using a Gaussian kernel to a smoothness of 8 mm FWHM. A high pass filter cut off of 50 seconds, as suggested by FSL, was used. The preprocessed fMRI data were then registered to a standard space using the FSL FLIRT program and the MNI152 brain as the reference image.

3.6 Functional Neuroimaging Data Analysis

Neuroimaging analyses were carried out using FEAT (FRMI Expert Analysis tool) Version 5.98 (FMRIB's Software Library www.fmrib.ox.ac.uk/fsl). General Linear Model (GLM) analyses of the fMRI were performed at 3 levels: block, subject and group. Four explanatory variables (EV) were entered at the block level for each subject. For example, one Other Player block included EVs for each of the following events: Suspiciousness no-risk, Suspiciousness risk, Rational Mistrust no-risk and Rational Mistrust risk. In the Suspiciousness no-risk EV, no financial risk Suspiciousness trials (*ad*≥$10) were coded '1' while all other trial types were coded as '0'. The hemodynamic response function was aligned with the presentation of the choice on each trial and ended with the selection of a choice. Using these 4 EVs, contrasts were modeled for a main effect of *adverse payoff* (*ad*) in each condition and interactions of *temptation***adverse payoff* at the block level. The statistical maps from the block level were then combined to create individual subject maps. In addition to the previously noted contrasts, a main effect of *decision-agent* (*da*) as well as *da*ad* and *da*t*ad* interactions were added to the model. Finally, the subject means were used to calculate group means for hypothesis testing.

Group analyses were limited to regions of interest identified in Chapter 2 by use of a mask (Figure 9). The regions were identified using the Harvard-Oxford Cortical and Subcortical Structural Atlas tool in FSLVIEW. The regions were merged together using FSLMATHS and then entered as a mask at the group level. A threshold of $p<.005$ uncorrected was applied to all voxels within the mask.

Figure 9. *Group Analysis Mask*



Note: Regions included in the group analysis mask included amygdala, insula, orbital frontal cortex, medial prefrontal cortex and paracingulate gyrus.

I tested for the relationship between Persecutory Ideation and neural activity by first identifying the group analysis of interest and creating masks for each area identified in the group contrast. I next extracted unthresholded Z-statistics from the subject-level version of the contrast. The raw mean unthresholded Z-statistics were then correlated with the measure Persecutory Ideation.

Chapter 4

Results

4.1 Participant Demographics

Participants had a mean age of 32.7 (SD=7.5) and were 69% men. Twenty-six participants were right-handed, 4 were left-handed and 2 reported no preference. Twenty-six participants were Caucasian, 4 were African-American, 1 was American Indian and 1 was Asian. Nineteen participants reported partial college, 7 reported a high school diploma or equivalent and 6 reported a Bachelor's degree from a 4-year college. Twenty-five of the participants were single, 6 were married and 1 was separated. Eleven of the participants were employed full or part-time, 16 were unemployed and 5 were students full or part-time. The mean raw Wechsler Adult Reading Test (WTAR) was 40/50 (SD=7.39).

4.2 Diagnoses and Symptom Ratings

Twenty-four participants had a diagnosis of Schizophrenia and 8 participants had a diagnosis of Schizoaffective Disorder. The overall Brief Psychiatric Rating Scale (BPRS) mean score indicated that participants were experiencing a very mild level of psychiatric symptoms at the time of data acquisition (Mean=2, SD=.44). Using a four-factor model of the BPRS (Ruggeri, 2005) this sample reported slightly more positive symptoms than affective or negative (Table 5).

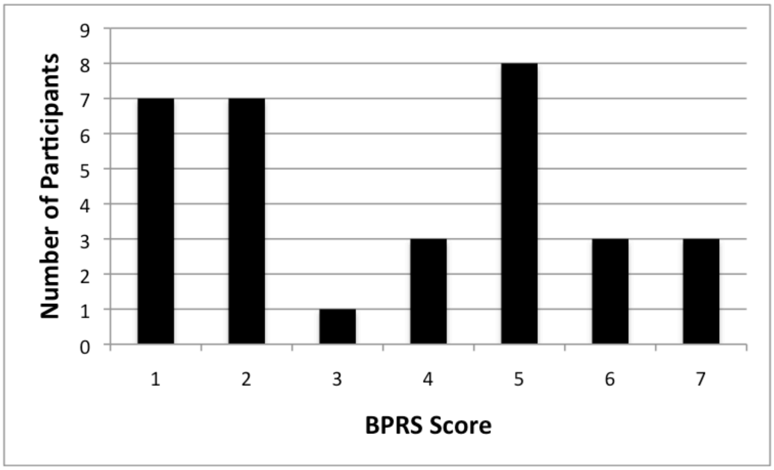
Table 5. *Brief Psychiatric Rating Scale Symptom Ratings*

BPRS Item	Rating	BPRS Item	Rating	Ruggeri Domain	Rating
Somatic Concern	2.03(1.38)	Self-neglect	2.31(1.28)	Manic-Excitement and Disorganization	1.46(0.31)
Anxiety	3.16(1.76)	Disorientation	1.22(0.55)	Anxiety-Depression	2.08(0.76)
Depression	2.19(1.51)	Conceptual Disorganization	2(1.19)	Negative Symptoms	2.07(0.97)
Suicidaility	1.31(0.82)	Blunted Affect	2.84(1.48)	Positive Symptoms *	2.81(1.12)
Guilt	1.97(1.33)	Emotional Withdrawal	1.72(1.14)		
Hostility	1.91(0.93)	Motor Retardation	1.66(1)		
Elevated Mood	1.03(0.18)	Uncooperative-ness	1.84(1.17)		
Grandiosity	2.88(2.2)	Tension	1.47(1.02)		
Persecutory Ideation	3.59(2.08)	Excitement	1.28(0.92)		
Hallucinations	3.06(2.31)	Distractibility	1.5(1.02)		
Unusual Thought Content	3.31(1.77)	Motor Hyperactivity	1(0)		
Bizarre Behavior	1.38(0.87)	Mannerisms and Posturing	1.29(1.01)		
		BPRS Total Mean	2(0.43)		

Note: Mean and standard deviation of items and factor symptom ratings from the Brief Psychiatric Rating Scale (BPRS). Rating anchors are 1=absent, 2=very mild, 3=Mild, 4=Moderate, 5=Moderately Severe, 6=Severe and 7=extremely severe. *The Ruggeri Positive Symptom factor was calculated without the Suspiciousness item.

The average BPRS Persecutory Ideation score was in the mild to moderate range (mean=3.29) with scores ranging from 1-7. The modal score was 5 (Figure 10). A score of 3 is mild and indicated that the participant described incidents in which others have harmed or wanted to harm him that sound plausible. A score of 6 is severely delusional and indicated that the participant spoke of mafia plots, the FBI or others poisoning him, or persecution by supernatural forces. Higher scores on Persecutory Ideation and other positive symptom items indicated a more bizarre presentation and a greater frequency and impact on behavior. See Appendix 4 for complete anchors for Persecutory Ideation item.

Figure 10. *Histogram of Brief Psychiatric Rating Scale Persecutory Ideation scores*



Note: 1=absent, 7=extremely severe

4.3 MTG Decision-making Results

4.3.1 Characterization of First Mover Decisions

No response rates, reaction times and percent of choices deferred in the Other Player and Risk Aversion conditions are presented in Table 6. The overall no response rate on the First Mover trials was 2 percent (SD=3%). The overall reaction time for First Mover trials was 2049 ms (SD=480). Two repeated measures ANOVAs with *decision-agent*, *temptation* and dichotomous *adverse payoff* as factors (2 x 2 x 2) were carried out to determine whether the task manipulations had an effect on no response rates and reaction times. There was a significant main effect of *decision-agent* on no response rate ($F(1,31)=4.28$, $p=.047$) such that participants were less likely to miss a response in the Risk Aversion conditions. There was a significant main effect of *decision-agent* on reaction time (F(1,31)=13.74, p<.001) such that participants responded faster in Risk Aversion conditions. No other significant main effects or interactions were observed.

Table 6. *No Response, Reaction Time and Choice from the MTG First Mover Game*

Trial Type	Proportion No Response	Reaction Time	Proportion Choices Deferred*
Risk Aversion 15	.01(0.03)	1856.92(494.86)	0.44(0.18)
Risk Aversion 25	0.02(0.03)	1858.58(456.7)	0.42(0.14)
Suspiciousness	0.03(0.05)	2220.53(684.22)	0.7(0.27)
Rational Mistrust	0.02(0.04)	2252.95(638.47)	0.42(0.19)
No Risk (*ad*≥$10)	0.02(0.03)	1938.06(474)	0.96(0.05)
Risk (*ad*≤$9)	0.02(0.04)	2096.26(524.91)	0.3(0.2)

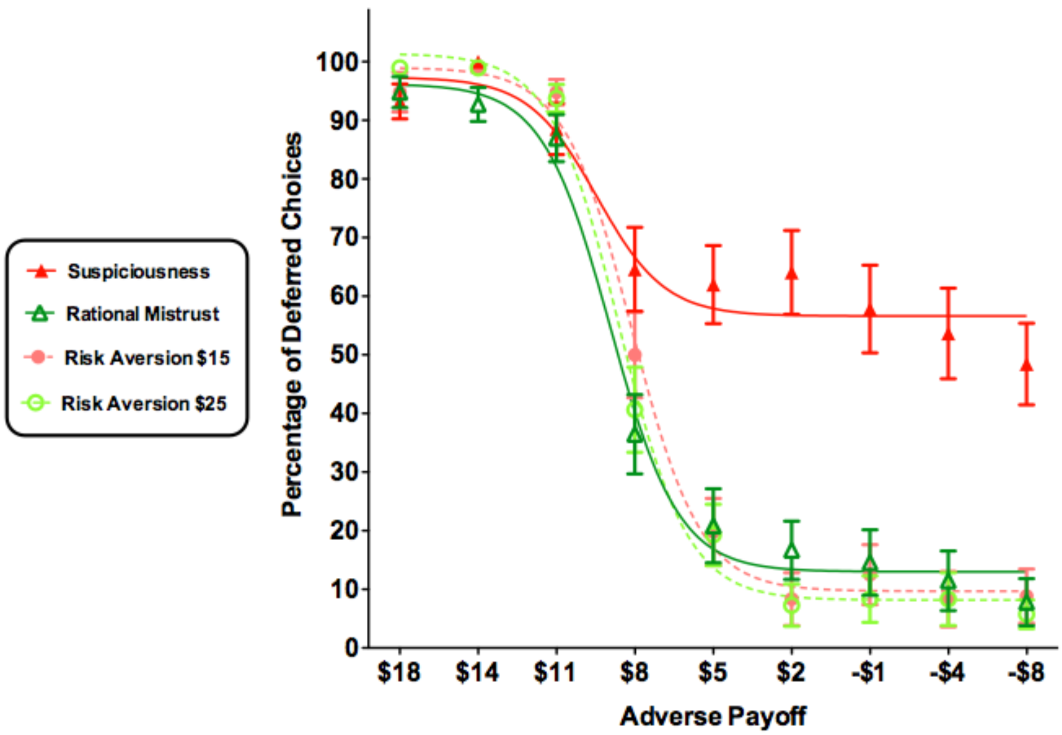
Note: Mean(Standard Deviation), *ad* = adverse payoff, Proportion Choices Deferred = proportion of choices the participant allowed the coin-flip or other player determine outcome.

A repeated-measures logistic regression of the task manipulations, *decision-agent (da)*, *temptation (t)*, and *adverse payoff (ad)* on choice as a First Mover resulted in the predicted three-way interaction of *da*t*ad* (ß = .013, p < .005) (Table 7 & Figure 11). Participants were less likely to trust in the Other Player with the increasing financial risk associated with the *adverse payoff* (OR = .532, 95% CI [.485, .583]). However, this effect was stronger in the Risk Aversion conditions (OR = .365, 95% CI [.265, .502]). Second, in the Other Player conditions, participants were less likely to trust when the *temptation* was equal to $25 as opposed to $15 (OR = .293, 95% CI [.186, .461]). However, the same effect of *temptation* was not found in the Risk Aversion conditions (OR = .936, 95% CI [.801, 1.095]). Finally, the level of the *adverse payoff* had differing effects depending on both the level of *temptation* and *decision-agent*. The likelihood of participants trusting the other player decreased with the mounting financial risk of the *adverse payoff* more in the Rational Mistrust condition (OR = .461, 95% CI [.360, .590]) than in the Suspiciousness condition (OR = .712, 95% CI [.657, .771]). A similar difference was not observed between the Risk Aversion 25 and 15 conditions ((OR = .337, 95% CI [.241, .472]); (OR = .389, 95% CI [.276, .550]), respectively). Thus, the analyses of basic effects reflected the hypothesized interactions among these three variables. These findings are consistent with our findings in controls and suggest that patients were able to understand the paradigm. See Appendix 5 for analysis of the Second Mover data.

Table 7. *Repeated measures logistic regression of MTG First Mover Decision*

Variable	**Coefficient**	**SE**	**95 % CI**	***p***
Full Model				
Constant	3.162	.351	2.473 to 3.851	.000
decision-agent	4.649	1.002	2.686 to 6.613	.000
temptation	-.013	.016	-.044 to .017	.399
adverse payoff	-.867	.107	-1.077 to -.657	.000
*decision-agent*temptation*	-.23	.049	-0327 to -.133	.000
decision-agent temptation* adverse payoff*	.013	.005	.003 to .022	.009
Other Player Trials				
Constant	2.274	.75	.804 to 3.744	.002
temptation	.01	.038	-.064 to .083	.796
adverse payoff	.313	.194	-.067 to .694	.107
temptation adverse payoff*	-.044	.012	-.068 to -.019	.000
Risk Aversion Trials				
Constant	2.728	.884	.995 to 4.461	.002
temptation	.034	.037	-.04 to .107	.369
adverse payoff	-.729	.308	-1.333 to -.126	.018
temptation adverse payoff*	-.014	.013	-.039 to .011	.263

Figure 11. *Line Graph of First Mover Choices by Decision-agent, Temptation and Adverse Payoff*



4.3.2 MTG Decision-making Results & Brief Psychiatric Rating Scale (BPRS) Persecutory Ideation

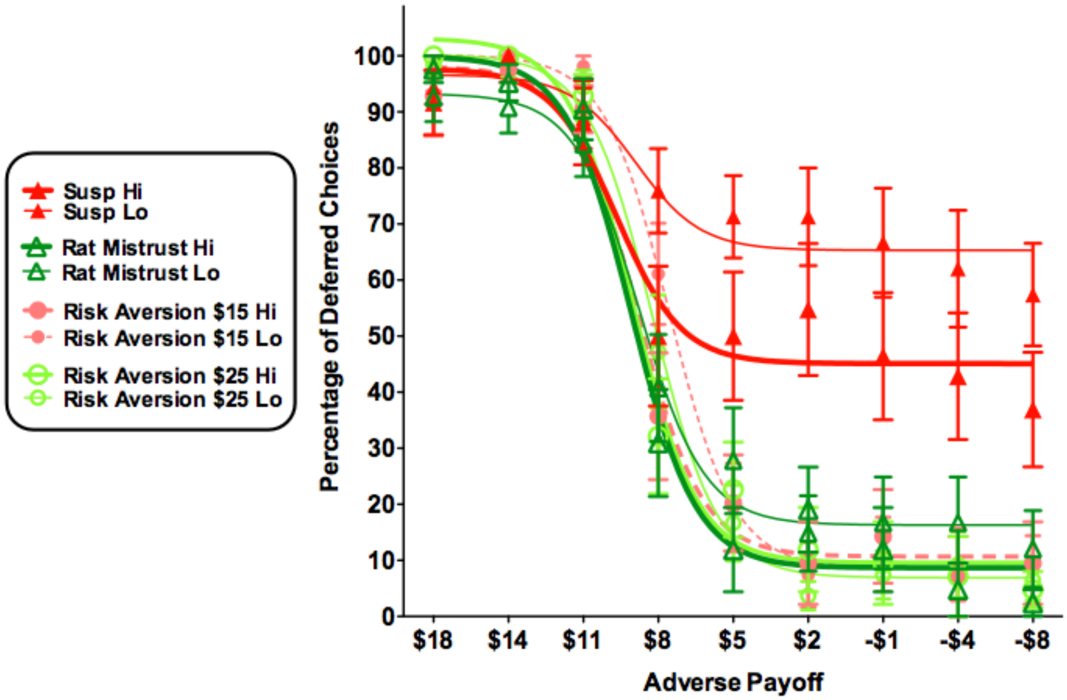
A repeated-measures logistic regression of Brief Psychiatric Rating Scale Persecutory Ideation and task manipulations on choice as a First Mover resulted in a significant three-way interaction of *decision-agent (da) by temptation (t) by Persecutory Ideation* (ß = .001, p = .015) (Table 8 & Figure 12). There was no interaction of *t* by Persecutory Ideation in the Risk Aversion conditions but there was a trend-level finding in the Other Player conditions. Though this finding was not significant, it merited further investigation to determine if the initial 3-way interaction was consistent with our hypothesis. Persecutory Ideation and *adverse payoff* (*ad*) were entered as predictors in a logistic regression restricted to the Suspiciousness condition. We found that Persecutory Ideation scores were associated with a decreased likelihood of trusting the Other Player only in the Suspiciousness condition (OR = .794, 90% CI [.60, .89]) (Figure 11). Note that the odds ratio for this finding is associated with an increase of one point on the Persecutory Ideation scale. So, on average a one-point increase on the Persecutory Ideation scale is associated with .79 times reduced likelihood of trusting the other player in the Suspiciousness condition. Behavior in the Suspiciousness condition was not predicted by scores on Ruggeri's positive symptom factor (ß =.290, $p = .114$) calculated without the Persecutory Ideation item.

Table 8. *Repeated Measures Logistic Regression of First Mover Choices and BPRS Persecutory Ideation*

Variable	Coefficient	SE	95 % CI	*p*
All Trials				
Constant	4.146	.592	2.986 to 5.306	.000
Decision-agent	1.355	.474	.425 to 2.285	.004
Temptation	-.073	.019	-.11 to -.037	.000
Adverse Payoff	-.761	.071	-.9 to -.623	.000
Persecutory Ideation	-.041	.104	-.245 to .162	.689
*Decision-agent*Persecutory Ideation*	.25	.217	-.174 to .675	.247
*Decision-agent*temptation*Persecutory Ideation*	-.023	.01	-.042 to -.005	.015
*Decision-agent*temptation*adverse Payoff*Persecutory Ideation*	.001	.001	0 to .003	.064
Coin Trials				
Constant	4.503	1.299	1.958 to 7.049	.001
Temptation	-.046	.051	-.147 to .054	.368
Adverse Payoff	-1.012	.166	-1.337 to -.687	.000
Persecutory Ideation	-.225	.292	-.798 to .347	.440
*Temptation*Persecutory Ideation*	.009	.01	-.012 to .029	.403
Other Player Trials				
Constant	8.491	1.675	5.207 to 11.775	.000
Temptation	-.27	.069	-.405 to -.135	.000
Adverse Payoff	-.542	.053	-.645 to -.439	.000
Persecutory Ideation	-.66	.332	-1.311 to -.009	.047
*Temptation*Persecutory Ideation*	.026	.014	-.001 to .053	.057
Rational Mistrust Trials				
Constant	2.55	.5	1.571 to 3.529	.000
Adverse Payoff	-.775	.126	-1.021 to -.528	.000
Persecutory Ideation	-.009	.105	-.215 to .197	.931
Suspiciousness Trials				
Constant	3.345	.000	2.185 to 4.505	.000
Adverse Payoff	-.354	.045	-.443 to -.265	.000
Persecutory Ideation	-.231	.121	-.352 to -.11	.023*

Note: *P-value reported is one-tailed with 90% CI.

Figure 12. *Line Graph of First Mover Choices by Decision-agent, Temptation and Adverse Payoff*



In summary, we were able to establish the three-way interaction of *decision-agent* (*da*) by *temptation* (*t*) by *adverse payoff* (*ad*). Suggesting that each of the three conditions were associated with different patterns of decision-making. Specifically, we found that the level of *ad* had differing effects depending on the level of *da* and *t*. The level of *ad* was a less powerful predictor of behavior in the Other Player condition as opposed to Risk Aversion. Additionally, within the Other Player conditions, the level of *ad* was a less powerful predictor in the Suspiciousness condition than Rational Mistrust. Finally, consistent with previous findings and hypotheses, we found that Persecutory Ideation was associated with behavior in the Other Player but not Risk Aversion conditions. Specifically, participants with higher levels of Persecutory Ideation were less likely to trust the other player in Suspiciousness condition but not Rational Mistrust. In the next section, we will explore these decision-making and symptom findings in the functional neuroimaging data.

4.4 Functional Neuroimaging Results

4.5.1 Effect of Condition greater than Fixation

We first looked for activation greater than fixation in each of the main conditions: Suspiciousness, Rational Mistrust and Risk Aversion (Table 9) within the a priori regions identified by the mask (see Figure 9 in Chapter 3). Overall, the contrasts showed similar patterns of activation. In all conditions, the paracingulate activation extended into the anterior cingulate cortex and superior frontal gyrus, and the bilateral amygdala activation was on the medial surface of the amygdala. In the Suspiciousness condition, the left amygdala activation extended dorsally to the globus pallidus. The activation in the Suspiciousness and Rational Mistrust conditions was in the anterior insula whereas the Risk Aversion insula activation covered both anterior and posterior regions of the insula. In all of the conditions, the orbital frontal cortex extended more anterior on the right then on the left. Calculation of mean Z-statistics extracted from the identified regions in each contrast indicated that all of the activations represented an increase from fixation. Thus there is broad evidence for task-related activity across conditions in nearly all the a priori regions identified in Chapter 2.

Table 9. *Effect of Condition Greater than Fixation in 3 Conditions of the Minnesota Trust Game within A Priori Regions of Interest.*

Region	BA	X	Y	Z	Voxels	Max Z
Suspiciousness						
Paracingulate Gyrus	32	-12	4	42	4058	8.031
Left Globus Pallidus/Amygdala	--	-14	-4	-10	363	4.834
Right Amygdala	--	18	-4	-12	459	4.724
Left Insula	13	-34	14	4	1670	5.737
Right Insula	13	32	20	2	1275	5.442
Right Orbital Frontal Cortex	11/47	34	28	0	2929	6.322
Left Orbital Frontal Cortex	11/47	-34	20	-10	1830	5.581
Rational Mistrust						
Paracingulate Gyrus	32	-8	20	36	3644	6.514
Left Amygdala	--	-16	-6	-12	151	2.783
Right Amygdala	--	18	-6	-12	231	2.630
Left Insula	13	-32	12	2	1049	5.859
Right Insula	13	34	18	-4	747	5.623
Left Orbital Frontal Cortex	47/11	-30	18	-12	1223	4.952
Right Orbital Frontal Cortex	47/11	36	28	-6	2421	6.065
Risk Aversion						
Paracingulate Gyrus	32	-2	14	44	3853	6.162
Left Amygdala	--	-18	-4	-12	100	3.076
Right Amygdala	--	18	-10	-12	242	2.894
Left Insula	13	-30	18	-2	869	5.329
Right Insula	13	34	18	-2	911	5.128
Right Orbital Frontal Cortex	47/11	16	12	-14	2706	6.082
Left Orbital Frontal Cortex	47/11	-32	18	-12	1310	4.546

Note: BA=Brodmann Area; x, y, z = location of the maximum z-statistic in the identified region of interest reported in Montreal Neurological Institute (MNI) space; Voxels=number of voxels activated within the mask; Max Z = maximum z-statistic of the identified region of interest.

4.4.2 Decision-agent by Financial Risk Activation

We next examined the differing effect of the financial risk (*adverse payoff*) on the Other Player and Risk Aversion trials. This contrast revealed multiple significant bilateral and midline brain regions (Table 10 & Figure 13). In the anterior cingulate and lateral orbital frontal cortex each condition entered into the contrast was associated with an increase from fixation. In the left amygdala the Other Player no financial risk (*adverse payoff* ≥ $10) condition showed a slight decrease. However, the max Z-statistics suggested that each condition was an increase from fixation and that the error bars on the Other Player conditions did not overlap (See Appendix 6).

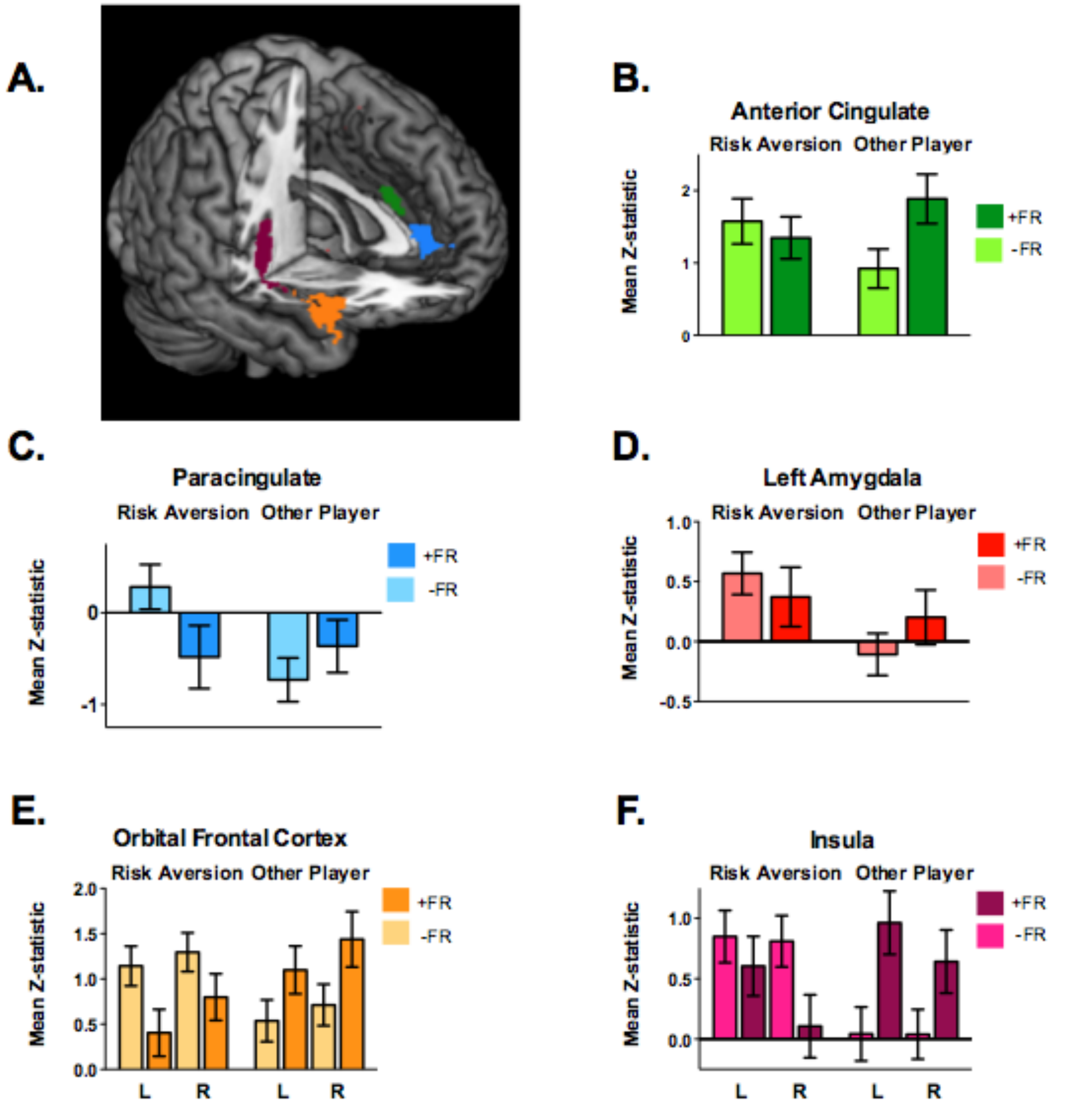
The paracingulate finding reflected a relative increase in the Other Player conditions such that financial risk was associated with less of a decrease than the no financial risk. This effect was in the opposite direction in the Risk Aversion condition and appeared to reflect a significant difference as indicated by the non-overlapping error bars. However, the max Z-statistics suggest that both conditions were an increase from fixation and that the Other Player financial risk was greater than the no financial risk condition (see Appendix 6). In the Risk Aversion conditions, financial risk showed less activation than the no financial risk condition. We also tested for activation in the Risk Aversion greater than Other Player contrast but this showed no activation.

Table 10. *Brain Region Activations in the Decision-agent by Financial Risk Contrast (Other Player greater than Risk Aversion)*

Region	BA	X	Y	Z	Voxels	Max Z
Caudal Anterior Cingulate Cortex	24	0	24	22	265	3.517
Paracingulate Cortex/Rostral Anterior Cingulate Cortex	32	0	42	6	179	3.531
Left Amygdala/Hippocampus	--	-24	-16	-12	168	2.597
Right Insula (Heschl's Gyrus)	13	42	-20	6	1009	4.079
Left Insula	13	-36	-14	8	1232	4.063
Right Orbital Frontal Cortex	47	48	24	-10	528	3.431
Left Orbital Frontal Cortex	--	-38	22	-16	302	2.618

BA=Brodmann Area; x, y, z = location of the maximum z-statistic in the identified region of interest reported in the Montreal Neurological Institute (MNI) space; Voxels=number of voxels activated within the mask; Max Z = maximum z-statistic of the identified region of interest.

Figure 13. *Decision-agent by Financial Risk Contrast*



Note: A. Brain image of areas where the Other Player financial risk trials showed greater activation than the Other Player no risk trials controlling for Risk Aversion. B-F. Bar graphs showing financial risk (+FR) (*adverse payoff* ≤$10) and no financial risk (-FR) (*adverse payoff* ≥$10) for the Other Player and Risk Aversion conditions for each area identified in the group *decision-agent* by *financial risk* contrast. The y-axis represents the mean unthresholded Z-statistics extracted from individual subject contrast maps.

4.4.3 Effect of Financial Risk in Suspiciousness, Rational Mistrust and Risk Aversion Conditions

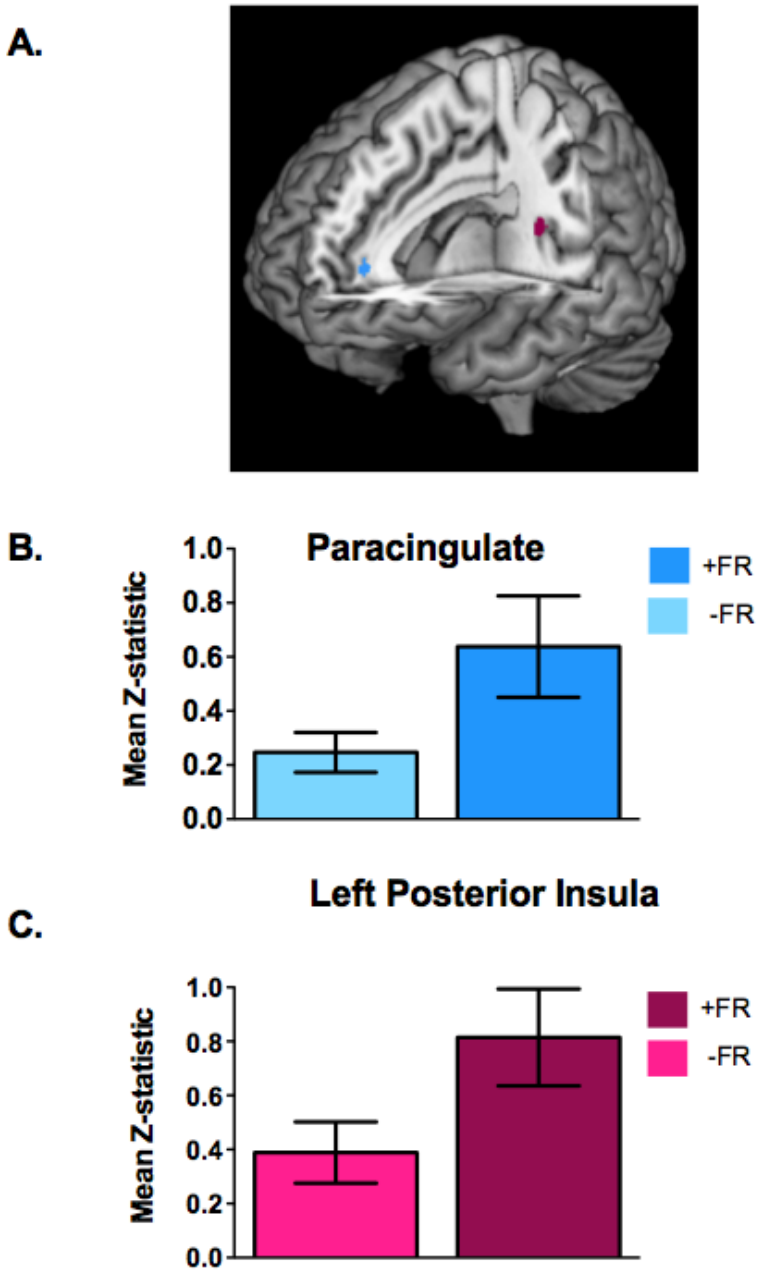
We next examined the effect of financial risk, as indicated by the *adverse payoff*, in each condition. The Suspiciousness contrast showed that financial risk was associated with greater activation in the paracingulate and left insula when deciding whether or not to trust another player with no financial incentive to betray (Table 11 & Figure 14). Both regions represent an increase from fixation. We also tested for activation in the Suspiciousness greater than Rational Mistrust contrast but this showed no activation.

Table 11. *Brain Region Activations in the Effect of Financial Risk Restricted to the Suspiciousness Condition*

Region	BA	X	Y	Z	Voxels	Max Z
Suspiciousness Condition						
Paracingulate	32	-12	42	6	41	2.95
Left Insula	13	-34	-22	16	54	3.276

BA=Brodmann Area; x, y, z = location of the maximum z-statistic in the identified region of interest reported in Montreal Neurological Institute (MNI) space; Voxels=number of voxels activated within the mask; Max Z = maximum z-statistic of the identified region of interest.

Figure 14. *Effect of Financial Risk Restricted to the Suspiciousness Condition*



Note: A. Brain image showing areas where the Suspiciousness financial risk trials showed greater activation than the Suspiciousness no risk trials. B & C. Bar graphs showing financial risk (+FR) (*adverse payoff* ≤$10) and no financial risk (-FR) (*adverse payoff* ≥$10) from the Suspiciousness condition for each area identified in the group contrast of financial risk restricted to the Suspiciousness condition. The y-axis represents the mean unthresholded Z-statistics extracted from individual subject contrast maps.

The effect of risk restricted to the Rational Mistrust condition showed that financial risk was associated with greater activation in the left insula (BA 13; x,y,z = -40, -18, 10; 542 voxels; Max Z = 4.14) when deciding whether or not to trust another player who had financial incentive to betray. We also tested for differences in the Rational Mistrust greater than Suspiciousness contrast but there was no activation.

The effect of risk restricted to the Risk Aversion trials showed that financial risk was associated with greater activation in the left insula (BA 13; x,y,z = -36, -20, 14 ; 720 voxels; Max Z =3.774) when deciding whether or not to take a chance.

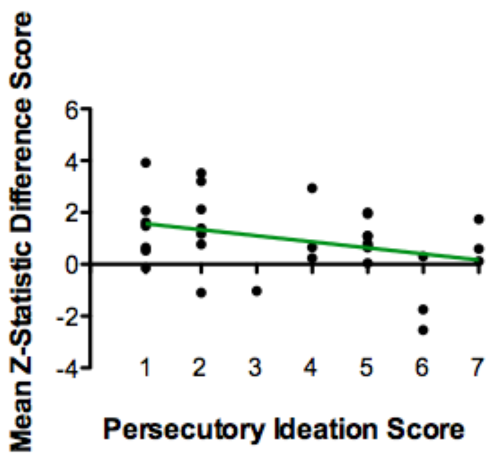
4.5 Neuroimaging Results and Brief Psychiatric Rating Scale Persecutory Ideation

We next examined the relationship between activation in the Other Player conditions and Persecutory Ideation ratings. There was a trend level relationship between increased financial risk and Persecutory Ideation in the anterior cingulate (r=.34, p=.056) such that higher Persecutory Ideation scores were associated with less sensitivity to financial risk in the Other Player but not Risk Aversion conditions (see Figures 13 A and B and Figure 15). We examined whether this effect was stronger in the Suspiciousness compared to Rational Mistrust condition. There was a trend level relationship between Persecutory Ideation and activation in the Suspiciousness financial risk greater than fixation contrast (r=.33, p=.066) but not in the Rational Mistrust financial risk greater than fixation contrast (r=.27, p=.128). These relationships were not significantly different in magnitude (z=.25, p=.8).

No other regions within the *decision-agent* by *financial risk* showed an association with Persecutory Ideation including the left amygdala, paracingulate, bilateral insula or orbital frontal cortex. We also examined if there was a relationship between

Persecutory Ideation and the effect of financial risk in the Suspiciousness and Rational Mistrust conditions. There was a modest trend level relationship between Persecutory Ideation and the effect of financial risk in the Suspiciousness condition in the paracingulate gyrus ($t(31)=1.65$, $p=.055$, one tailed) (See Appendix 6) but no relationship with left insula activation in either condition.

Figure 15. *Persecutory Ideation and Anterior Cingulate Activation*



Note: The scatter plot shows the Mean z-statistic from the Other Player Risk conditions minus the Other Player No Risk Condition in the Anterior Cingulate Cortex as identified by the *decision-agent* by *financial risk* contrast (Figure 12a & b) on the y-axis and Persecutory Ideation as measured by the Brief Psychiatric Rating Scale on the x-axis.

Chapter 5

Discussion & Conclusions

This study investigated the behavioral and neural correlates of Persecutory Ideation in a sample of patients with schizophrenia using an economic decision-making paradigm. Behavioral results from the Minnesota Trust Game (MTG) showed that our sample of patients with schizophrenia were sensitive to the task manipulation in a manner consistent with our hypothesis. Persecutory Ideation showed a specific relationship with mistrusting someone who has no financial incentive to betray, though this was a one-tailed test. With regards to functional neuroimaging results, the anterior cingulate, paracingulate, left amygdala, bilateral insula and orbital frontal cortex were specifically related to decision-making processes involving another person, regardless of their incentive to betray. Decisions involving trusting someone without incentive to betray were associated with activation in the paracingulate cortex and posterior left insula. Finally, we found a trend-level relationship between Persecutory Ideation and activity in the anterior cingulate cortex that suggested patients with persecutory ideation were less sensitive to financial risk associated with another person as opposed to chance.

5.1 Discussion of Decision-making findings

Results from the current study are consistent with our previous work using the Minnesota Trust Game (MTG) (M.K. Johnson, Duquette, Steen, & MacDonald III, 2009; M.K. Johnson & MacDonald III, 2009; M.K. Johnson, Rustichini, et al., 2009; MacDonald, et al., 2008). The 3-way interaction of *decision-agent (da)* by *temptation (t)* by *adverse payoff (ad)* we found in patients is the hallmark of task comprehension in the MTG. This result indicates that the translation of the MTG into a patient sample was successful. Indeed, the effect of *t* in the Other Player conditions was more robust than in a sample of healthy undergraduates (M.K. Johnson, Rustichini, et al., 2009). Patient's ability to modulate their decision-making behavior based on the other player's motives is a sign of intact theory of mind in this sample.

The effect sizes in the current study and our sample of twins recruited from the community are similar. For example, the effect size of financial risk on choices was medium to large in the Risk Aversion conditions (Cohen's d = -.861 and -.76) and small to medium in the Other Player conditions (Cohen's d = - .36 and -.4). Though we cannot make head-to-head comparisons, the similarity in patterns and sizes of effects in twins and patients improves our ability to make comparisons between the groups.

Prior to the current study the relationship between behavior in the Suspiciousness condition and personality measures of persecution ideation had been replicated in two samples of undergraduates and the sample of monozygotic twins. However, it was not clear if the type of persecutory ideation observed in patients was some how qualitatively different from suspiciousness as measured by instruments developed in normal samples. These results show that the Suspiciousness condition was able to account for variance in Persecutory Ideation as measured by the Brief Psychiatric Rating Scale (BPRS). This provides support for the idea that persecutory ideation in patients and persecuted personality styles in the general population are not qualitatively different phenomenon as measured by the MTG.

5.2 Discussion of Neuroimaging Findings

5.2.1 Ventromedial Prefrontal Cortex

We predicted that ventromedial prefrontal cortex (vmPFC) would be associated with decision-making in the Other Player greater than Risk Aversion contrast (*decision-agent* by *financial risk)* since mentalizing is needed in the former. Additionally, we predicted that the Suspiciousness greater than Rational Mistrust (*temptation* by *financial risk*) contrast would reveal vmPFC because of the Suspiciousness condition's relationship to Persecutory Ideation, a variant of self-referential thinking. However, in the current study we did not find activation in the vmPFC in any contrast.

One reason for the lack of vmPFC activity may be the relatively high degree of Persecutory Ideation in the sample. If Persecutory Ideation is associated with less vmPFC activity then it stands to reason that our sample may not on average show increased activation. In a study of trust in schizophrenia, Persecutory Ideation patients showed significantly less activation in a proposed social cognition network including the MPFC, left superior temporal sulcus, left fusiform gyrus, amygdala and ventrolateral prefrontal cortex compared to controls or non-Persecutory Ideation patients (Pinkham, Hopfinger, Ruparel, et al., 2008). It is important to note that in a sample of 46 monozygotic twins with high levels of persecuted personality, we found vmPFC (MacDonald, et al., 2008) (See Chapter 2, Figure 5). Another possibility is that schizophrenia patients' neural responses are not as sensitive to Minnesota Trust Game (MTG) task manipulations as controls. If this is the case, it certainly was not reflected in their behavioral performance.

5.2.2 Paracingulate Cortex

We observed the paracingulate cortex (PcC) in the *decision-agent* by *financial risk* contrast (See Chapter 4, Figure 12C). This finding was consistent with many studies that have implicated the PcC in conceptualizing the intentions of others (Gallagher, Jack, Roepstorff, & Frith, 2002; Krueger, et al., 2007; Walter et al., 2004). Combined with the behavioral results, the PcC findings support our prediction that patients would have intact theory of mind and would use it to conceptualize the other player's intentions as a means of guiding decision-making.

Similar to our sample of twins, increased PcC activity was associated with deciding whether or not to trust another player with no financial incentive to betray. We interpreted both of these findings as increased processing associated with trying to conceptualize the other player's disincentive to betray. It is important to note that the PcC activation in twins was the result of the Suspiciousness greater than Rational Mistrust contrast (*temptation* by *financial risk*) (see Chapter 2, Figure 5). In patients this same contrast showed no activation so we examined the effect of financial risk in the Suspiciousness condition (See Chapter 4, Figure 13B).

5.2.3 Orbital Frontal Cortex

We observed lateral orbital frontal cortex (OFC) in the *decision-agent* by *financial risk* contrast (See Chapter 4, Figure 12E). In our sample of twins, OFC activation was found in the Suspiciousness greater than Rational Mistrust contrast (*temptation* by *financial risk*) (see Chapter 2, Figure 5). This same contrast revealed no activation in patients. One explanation for this finding in twins was that Suspiciousness trials required a change in strategy in order to take advantage of the likely financial gains in the Suspiciousness condition. This explanation was less applicable in patients.

The lateral areas of BA 47 found in the *decision-agent* by *financial risk* contrast have been associated with prediction of punishment (Kringelback & Rolls, 2004). In Risk Aversion financial risk trials, participants were reticent to take the coin flip (16%) thus taking the OFC offline. In other words, they were certain to receive the *assured payoff* and not the *adverse payoff*. On the other hand, during financial risk Other Player trials, participants showed a willingness to trust the other player (38%) and were aware of the potential for punishment with financial loss. If this interpretation is true, then it suggests that this process represents relatively intact functioning compared to many reported deficits in the reward system (Gold, Waltz, Prentice, Morris, & Heerey, 2008 ; Heerey, Matveeva, & Gold, 2011)

5.2.4 Anterior Cingulate Cortex

In the current study we found that anterior cingulate cortex and paracingulate cortex were activated when the *decision-agent* was another player but not the coin (*decision-agent* by *financial risk*). This ACC activity was related to level of Persecutory Ideation such that participants with Persecutory Ideation were less sensitive to financial risk.

Studies using a version of the trust game, the ultimatum game, have reliably shown activation in these same regions (Chiu et al., 2008; Delgado, 2005; B. King-Casas, Tomlin, D., Anen, C., Camerer, C.F., Quartz, S.R., Montague, R.P. , 2005; A. G. Sanfey, et al., 2003; Tomlin, et al., 2006). In the ultimatum game an investor is endowed with a sum of money and asked to pass some proportion of that money on to a trustee. In the process of the exchange the proportion of the endowment passed is multiplied by some factor. The trustee then has the choice of returning some portion of the multiplied endowment back to the investor.

Chiu (2008) found rostral ACC/PcC activity in the trustee's brain when the investor's decision was revealed and middle ACC activity in the trustee's brain when his return of the endowment was revealed. In another protocol included in the study, rostral ACC/PcC activation was associated with the participant imagining someone else performing a motor activity, while middle ACC was associated with participant imagining his own motor activity. Remarkably, the ultimatum game findings from this study map *exactly* onto the findings from the visual imagery paradigm. The ACC region in our study maps onto the rostral portion of Chiu's middle ACC particle while our PcC region maps onto Chiu's rostral ACC/PcC

The authors concluded that the trustee's middle ACC activity was associated with self-referential processing of their own choice while the rostral ACC/PcC activity was associated with processing of the investor's choice. Of particular importance is that the activation in these regions is not specific to role (Investor vs. Trustee) (Tomlin, et al., 2006). In other words, the investor showed the exact same middle ACC activity when his decision was revealed. Why would the First Mover in the MTG show this pattern of activation in the decision-making phase? One possibility is that the First Mover needs to represent both his own role and the role of the other player in the decision-making process of the social exchange.

Chiu (2008) also included twelve high functioning adolescents with Autism as trustees in the study. Participants with Autism showed normal rostral ACC/PcC activity when the investor's response was revealed but showed greatly diminished activity in the middle ACC when their choice was revealed despite intact performance. This reduced activity in the middle ACC was correlated with symptom severity. The authors concluded that the social deficits in autism might not be associated with theory of mind but rather the ability to conceptualize one's own intentions and behaviors.

Why would higher levels of Persecutory Ideation be associated with decreased activation in a region of the ACC associated with conceptualizing one's own intentions and behaviors? One possibility is that patients with persecutory ideation experience a reduced sense of agency and therefore attribute events to other individuals or forces, a finding supported by the literature (S. Kaney & Bentall, 1989; Kinderman & Bentall, 1996, 1997). It is worth noting the similarities between individuals with schizophrenia and Autism. Individuals with Autism show heightened levels of persecution compared to the general population (North, Russell, & Gudjonsson, 2008) and in one study showed levels similar to paranoid schizophrenia (Pinkham, Hopfinger, Pelfrey, et al., 2008). Autism is also associated with attributional biases (Blackshaw, Kinderman, Hare, & Hatton, 2001).

5.2.5 Insular Cortex

This study found bilateral insula in the *decision-agent* by *financial risk* contrast and left posterior insula when examining the effect of risk in Suspiciousness, Rational Mistrust and Risk Aversion. More anterior regions were associated with risky choices involving another person whereas posterior regions did not show this specificity. Paulus (2003) found anterior insula when contrasting risky versus safe choices but only posterior left insula (x=-38, y=-21, z=15) when controlling for punishment. This suggests that the posterior insula has a specific relationship with the potential for negative outcomes. The anterior insula on the other hand has been associated with judging another person (Delgado, 2005; A. G. Sanfey, et al., 2003) but not necessarily taking a risk. In the case of the MTG this may reflect judging the likelihood that another person will betray.

5.2.6 Amygdala

The current study found that left amygdala was associated with deciding to trust another player regardless of their incentive to betray (*decision-agent* by *financial risk*). We had predicted that the amygdala would be activated in the Rational Mistrust greater than Suspiciousness contrast (*temptation* by *financial risk*). Though we did run this contrast, it revealed no activation. We also examined the effect of financial risk within the Rational Mistrust condition, which did not reveal amygdala activation. The absence of an amygdala finding may have been a function of reduced amygdala activation in schizophrenia patients with Persecutory Ideation (Pinkham, Hopfinger, Pelfrey, et al., 2008; Pinkham, Hopfinger, Ruparel, et al., 2008; Williams, et al., 2004a; Williams, et al., 2007).

The amygdala finding in *decision-agent* by *financial risk* contrast could have been associated with the appraisal of a potential financial loss at the hands of the other player (R. Adolphs, Tranel, D., & Damasio, A.R., 1998; Winston, et al., 2002). Alternatively, it could have been associated with linking stimuli with social or emotional values (R. Adolphs, 2001). In the latter case, the amygdala could be involved with linking the financial values on the screen with either participant's or the other player's emotional reaction. Given the fact that we did not find amygdala activation in twins and that we did not find activation in our predicted contrast, we were left with little interpretive leverage particularly with respect to the finding's implications for patients.

5.3 Potential concerns and Limitations

The current study found no activation when contrasting the Risk Aversion conditions vs. the Other Player. One possible explanation for this could be that participants took significantly longer to respond during the Other Player trials. As a result, the activation in the Other Player greater than Risk Aversion contrast could have been the result of increased time processing the decision as opposed to task specific differences. However, the hemodynamic response function was aligned with the presentation of the choice on each trial and ended with the selection of a choice. Therefore, the duration of each choice was accounted for in the regressors and could not have accounted for differences in activation.

Given that the twin sample was substantially larger (n=46), it is possible that collection of more data would have improved our ability to detect our predicted effects. Unfortunately, it is difficult to use the effect sizes from the twin study as a guidepost because of the statistical methods used in the neuroimaging data to correct for the non-independence of twin pairs. Desmond and Glover (2001) suggest that at least 20-25 participants are necessary to achieve 80% power when correcting for multiple comparisons within normal populations. It is quite likely that larger sample sizes are needed in psychiatric samples.

Finally, the absence of a control group was part of this study's design in order increase our power to detect processes specific to persecution, while controlling for other symptoms and factors (such as treatment effects and generalized deficits) relevant to patients' performance. Though we can make general comparisons between the sample of twins and patients, without a control group we are limited in our ability to make interpretations related to disease processes in schizophrenia. For example, generally speaking we found less activation in patients than we did in twins. This could be a result of inadequate power or it is possible that this sample of patients showed less robust activation than twins for reasons related to disease processes.

5.4 Conclusions and Future Directions

The current research took a novel approach to studying a symptom dimension of schizophrenia, Persecutory Ideation. To the best of our knowledge, this is the first study to use an economic decision-making paradigm in individuals with schizophrenia. We were able to establish the predicted decision-making and individual differences effects without compromising the validity of the paradigm. This was a major accomplishment in this study.

The current study's findings are not limited to methodological advances. Our results provide substantive insight into the cognition behind Persecutory Ideation. Chapter 1 of this manuscript stated that current measures of persecutory ideation in patients either lacked adequate reliability and specificity or were not conducive to functional neuroimaging in patients with schizophrenia. The basic and individual differences findings associated with the MTG have now been found in 2 samples of undergraduates (n=72 and n=243), 1 sample of monozygotic twins from the community (n=46) and a sample of patients with schizophrenia (n=32). The results from the current study have also clarified what persecutory ideation is not. First, Persecutory Ideation did not appear to be an excess or lack of Theory of Mind since Persecutory Ideation did not predict behavior in the Rational Mistrust condition. Second, there was no evidence of a probabilistic reasoning bias or a general aversion to risk since Persecutory Ideation did not predict behavior in the Risk Aversion conditions. Finally, the functional neuroimaging results from this sample of patients showed many similarities to a sample of twins, suggesting that the Minnesota Trust Game is conducive to neuroimaging in patients with schizophrenia.

In both control and patient samples, Persecutory Ideation predicted less trusting behavior when the other player had no financial incentive to betray. Put another way, this decision-making bias reflects a belief that other people are willing to incur costs to cause the participant harm. From a cognitive therapy perspective, this could be described as a core belief common to patients with Persecutory Ideation. Future interventions could target Persecutory Ideation by challenging the functionality or accuracy of such core beliefs.

In terms of neuroimaging results, we found that Persecutory Ideation was associated with reduced anterior cingulate cortex (ACC) activation when making a decision whether or not to trust another person. Chiu, et al. (2008) found a spatial arrangement of neural activation in the ACC that corresponded to self-referential and other referential processes. Activation associated with self-referential processes was severely diminished in men with Autism. Future research using the MTG in patients with schizophrenia may wish to narrow its focus to the ACC. For example, could spatial arrangement in the ACC be replicated in a sample of patients with schizophrenia? Also, future research may wish to include an executive functioning paradigm in order to compare where activation from the two tasks differ.

Future research could approach other types of delusional thinking using economic decision-making paradigms. The current line of research studied trust and persecuted personality traits in healthy individuals in order to improve our understanding of Persecutory Ideation in schizophrenia. A new line of research could study altruism using a variant of the Ultimatum Game to understand narcissism. Such a line of research may develop our understanding of grandiose delusions. Finally, our findings suggest that the integration of psychiatry and economic Game Theory can produce fruitful results.

References

Adolphs, R. (2001). The neurobiology of social cognition. *Curr Opin Neurobiol, 11*, 231-239.

Adolphs, R., Tranel, D., & Damasio, A.R. (1998). The human amygdala in social judgement. *Nature, 393*, 470-474.

Allardyce, J., Gaebel, W., Zielasek, J., & van Os, J. (2007). Deconstructing Psychosis Conference February 2006: The Validity of Schizophrenia and Alternative Approaches to the Classification of Psychosis. . *Schizophr Bull, 33*(4), 863–867.

American-Psychiatric-Association (Ed.). (2000). *Diagnostic and Statistical Manual of Mental Disorders* (Fourth, Text Revision ed.). Washington, D.C.: American Psychiatric Association.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience, 7*, 268-277.

Andreasen, N. C., Arndt, S., Alliger, R., Miller, D., & Flaum, M. (1995). Symptoms of schizophrenia: Methods, meanings, and mechanisms. *Arch Gen Psychiatry, 52*, 341-351.

Andreasen, N. C., & Olsen, S. (1982). Negative v Positive Schizophrenia. *Arch Gen Psychiatry, 39*, 789-794.

Appelbaum, P. S., Robbins, P. C., & Roth, L. H. (1999). Dimensional approach to delusions: Comparison across types and diagnoses. *American Journal of Psychiatry, 156*(12), 1938-1943.

Arseneault, L., Moffit, T. E., Caspi, A., Taylor, P. J., & Silva, P. A. (2000). Mental disorders and violence in a total birth cohort. *Archives of General Psychiatry, 57*, 979-986.

Athanasiadis, L. (1997). Greek mythology and medical and psychiatric terminology. *Psychiatric Bulletin, 21*, 781-782.

Barch, D., Carter, C., MacDonald, A., Braver, T., & Cohen, J. (2003). Context processing deficits in schizophrenia: Diagnostic specificity, four-week course, and relationships to clinical symptoms. *Journal of Abnormal Psychology, 112*, 132-143.

Bentall, R. P., Rowse, G., Shryane, N., Kinderman, P., Howard, R., Blackwood, N., et al. (2009). The Cognitive and Affective Structure of Paranoid Delusions A Transdiagnostic Investigation of Patients With Schizophrenia Spectrum Disorders and Depression
. *Arch Gen Psychiatry, 66*(3), 236-247.

Berg, J. (1995). Trust, reciprocity, and social history. *Games and Economic Behavior, 10*, 122-142.

Blackshaw, A. J., Kinderman, P., Hare, D. J., & Hatton, C. (2001). Theory of mind, causal attribution and paranoia in Asperger syndrome. *Autism, 5*(2), 147-163.

Blackwood, N. J., Howard, H.J., Bentall, R.P., Murray, R.M. (2001). Cognitive neuropsychiatric models of persecutory delusions. *American Journal of Psychiatry, 158*, 527-539.

Bleuler, E. (1950). *Dementia praecox or the group of schizophrenias* (T. b. J. Zinkin, Trans.). New York: International Universities Press (Original work published 1911).

Bohnet, I., & Zeckhauser, R. (2004). Trust, risk and betrayal. *Journal of Behavior and Organization, 55*, 467-484.

Bottlender, R., Jager, M., Strauss, A., & Moller, H. J. (2000). Suicidality in bipolar compared to unipolar depressed inpatients. *European Archives of Psychiatry & Clinical Neuroscience., 250*(5), 257-261.

Butcher, J. N. W., C.L. (2000). *Essentials of MMPI-2 and MMPI-A Interpretation* (2 ed.). Minneapolis, MN: University of Minnesota Press.

Carpenter, W. T. (2007). Schizophrenia: Disease, Syndrome, or Dimensions? *Family Process, 46*(2), 199-206.

Carpenter, W. T., Heinrichs, D. W., & Wagman, A. M. (1988). Deficit and nondeficit forms of schizophrenia: The concept. *American Journal of Psychiatry, 145*(5), 578-583.

Carpenter, W. T., J.J., B., Carpenter, C. L., & Strauss, J. S. (1976). Another View of Schizophrenia Subtypes: a Report from the International Pilot Study of Schizophrenia. *Arch Gen Psychiatry, 33*, 508-516.

Chiu, P. H., Kayali, A., Kishida, K. T., Tomlin, D., Klinger, L. G., Klinger, M. R., et al. (2008). Self Responses along Cingulate Cortex Reveal Quantitative Neural Phenotype for High-Functioning Autism. *Neuron, 57*, 463-473.

Cohen, J. D., Barch, D. M., Carter, C. S., & Servan-Schreiber, D. (1999). Context-processing deficits in schizophrenia: Converging evidence from three theoretically motivated cognitive tasks. *Journal of Abnormal Psychology, 108*(1), 120-133.

Cohen, J. D., & Servan-Schreiber, D. (1992). Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychological Review, 99*(1), 45-77.

Cook, W., & Medley, D. (1954). Proposed hostility and parisaic-virtue scales for the MMPI. *Jounral of Applied Psychology, 38*, 414-418.

Corcoran, R., Cummins, S., Rowse, G., Moore, E., Blackwood, N., Howard, R., et al. (2006). Reasoning under uncertainty: heuristic judgments in patients with persecutory delusions or depression. *Psychol Med, 36*(8), 1109-1118.

Corcoran, R., Mercer, G., & Frith, C. D. (1995). Schizophrenia, symptomatology and social inference: Investigation 'theory of mind' in people with schizophrenia. *Schizophrenia Research, 17*, 5-13.

D'Argembeau, A., Collette, F., Van der Linden, M., Laureys, S., Del Fiore, G., Degueldre, C., et al. (2005). Self-referential reflective activity and its relationship with rest: a PET study. *Neuroimage, 25*, 616-624.

David, N., Bewernick, B. H., Cohen, M. X., Newen, A., Lux, S., Fink, G. R., et al. (2006). Neural Representations of Self versus Other: Visual–Spatial Perspective Taking and Agency in a Virtual Ball-tossing Game. *Journal of Cognitive Neuroscience, 18*(6), 898–910.

Delgado, M. R., Frank, R.H., & Phelps, E.A. . (2005). Perceptions of moral character modulate the neural system of reward during a trust game. *Nature Neuroscience, 8*(11), 1611-1618.

Dikeos, D., Wickham, H., McDonald, C., WALSHE, M., SIGMUNDSSON, T., BRAMON, E., et al. (2006). Distribution of symptom dimensions across Kraepelinian divisions. *Br J Psychiatry, 189*, 346-353.

DiLalla, D. L., & Gottesman, I. I. (1995). Normal personality characteristics of identical twins discordant for schizophrenia. *Journal of Abnormal Psychology, 104*(3), 490-499.

Eckel, C. C., & Wilson, R. K. (2004). Is trust a risky decision? *J. of Economic Behavior & Org, 55*(4), 447–465.

Elliott, R., Dolan, R. J., & Frith, C. D. (2000). Dissociable functions in he medial and lateral orbitofrontal cortex: Evidence from human neuroimaging studies. *Cerbral Cortex, 10*, 308-317.

Feighner, J. P., Robins, E., Guze, S. B., Woodrmff, E. A., Winokur, G., & Munoz, R. (1972). Diagnostic Criteria for Use in Psychiatric Research. *Arch Gen Psychiatry, 26*, 57-63.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute.

Freeman, D., Garety, P. A., Bebbington, P. E., Smith, B., Rollinson, R., & Fowler, D. (2005). Psychological investigation of the structure of paranoia in a non-clinical population. *British Journal of Psychiatry, 186*, 427-435.

Freeman, D. G., P.A. (2004). *Paranoia: The Psychology of Persecutory Delusions*. East Sussex: Psychology Press.

Frith, C. D. (2004). Schizophrenia and theory of mind. *Psychological Medicine, 34*, 385-389.

Fuchs, T. (1992). Life events in late paraphrenia and depression. *Psychopathology, 32*, 60-69.

Gallagher, H. L., Jack, A. I., Roepstorff, A., & Frith, C. D. (2002). Imaging the intentional stance in a competitive game. *Neuroimage, 16*, 814-821.

Gold, J. M., Waltz, J. A., Prentice, K. J., Morris, S. E., & Heerey, E. A. (2008). Reward processing in schizophrenia: a deficit in the representation of value. *Schizophr Bull. , 34*(5), 835-847.

Gunnthorsdottir, A., McCabe, K., & Smith, V. (2002). Using the Machiavellianism instrument to predict trustworthiness in a bargaining game. *Journal of Economic Psychology, 23*, 59-66.

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *PNAS, 98*(7), 4259–4264.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience, 2*(10), 685-964.

Han, K., Weed, N. C., Calhoun, R. F., & Butcher, J. N. (2000). Psychometric Charateristics of the MMPI-2 Cook-Medley Hostility Scale. In J. N. Butcher (Ed.), *Basic Sources on the MMPI-2*. Minneapolis: University of Minnesota Press.

Hathaway, S. R., & McKinley, J. C. (1940). A multiphasic personality schedule (Minnesota): I. Construction of the schedule. *Journal of Psychology, 10*, 249-254.

Haut, K. M., Lim, K. O., & MacDonald, A. W. I. (2010). Prefrontal Cortical Changes Following Cognitive Training in Patients with Chronic Schizophrenia: Effects of Practice, Generalization, and Specificity. *Neuropsychopharmacology, 35*, 1850-1859.

Heerey, E. A., Matveeva, T. M., & Gold, J. M. (2011). Imagining the future: degraded representations of future rewards and events in schizophrenia. *J Abnorm Psychol, 120*(2), 483-439.

Hemsley, D., & Garety, P. (1986). Formation and maintenance of delusions: a Bayesian analysis. *Br J Psychiatry, 149*, 51–56.

Heretick, D. M. L. (1981). Gender-specific relationships between trust-suspicion, locus of control and psychological distress. *Journal of Psychology, 108*, 267-274.

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III -- The final common pathway. *Schizophr Bull, 35*(3), 549-562.

Huber, D., Veinante, P., & Stoop, R. (2005). Populations in the Central Amygdala Vasopressin and Oxytocin Excite Distinct Neuronal. *Science, 308* (8), 245-248.

Janssen, I., Hanssen, M., Bak, M., Bijl, R. V. , de Graaf, R., & Vollenberg, W. (2003). Discrimination and delusional ideation. *British Journal of Psychiatry, 182*, 71-76.

Johnson, M. K., Duquette, S., Steen, M., & MacDonald III, A. W. (2009). A Multiple Method Study Explores Personality Traits and Decision-making Biases Associated with Persecution, Cynicism, and Hostility, *Poster presented at the Society for Research in Psychopathology*. Minneapolis, MN.

Johnson, M. K., & MacDonald III, A. W. (2009). Economic decision-making task behavior predicts discordance of persecutory ideation, *Poster presented at the Behavioral Genetics Society*. Minneapolis, MN.

Johnson, M. K., Rustichini, A., & MacDonald, A. W., III. (2009). Suspicious personality predicts behavior in a social decision-making task. *Personality and Individual Differences, 47*, 30–35.

Johnson, M. K., Walter, R., Carter, C. S., & MacDonald, A. W. (2007). Dissociating the Neural Basis of Suspiciousness from Rational Mistrust and Risk Aversion: An fMRI Study of the Minnesota Trust Game, *Poster presented at the 11th Biennial International Congress of Schizophrenia Research*. Colorado Springs, CO.

Johnson, S. C., Baxter, L. C., Wilder, L. S., Pipe, J. G., Heiserman, J. E., & Prigatano, G. P. (2002). Neural correlates of self-reflection. *Brain, 125*, 1808-1814.

Kahneman, D. T., A. (1979). Prospect theory: An analysis of decision under risk. *Econometrica, 47*(2), 263-292.

Kaney, S., & Bentall, R. P. (1989). Persecutory delusions and attributional style. *British Journal of Medical Psychology, 62*, 191-198.

Kaney, S., Bowen-Jones, K., Dewey, M., & Bentall, R. (1997). Two predictions about paranoid ideation: deluded, depressed and normal participants' subjective

frequency and consensus judgments for positive, neutral and negative events. . *Br J Clin Psychol, 36*(3), 349-364.
Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., lnati, S., & T.F., H. (2002). Finding the self: An event-related fMRI study. *Journal of Cognitive Neuroscience, 14*(785-794).
Kerns, J., & Berenbaum, H. (2002). Cognitive impairments associated with formal thought disorder in people with schizophrenia. *Journal of Abnormal Psychology, 111*(2), 211-224.
Kinderman, P., & Bentall, R. P. (1996). A new measure of causal locus: the internal, personal and situational attributions questionnaire *Personality and Individual Differences, 20*(2), 261-264.
Kinderman, P., Bentall, RP. (1997). Causal attributions in paranoia and depression: internal, personal, and situational attributions for negative events. *Journal of Abnormal Psychology, 106*(103-107).
King-Casas, B., Sharp, C., Lomax-Bream, L., Lohrenz, T., Fonagy, P., & Montague, P. R. (2008). The Rupture and Repair of Cooperation in Borderline Personality Disorder. *Science, 321*, 806-810.
King-Casas, B., Tomlin, D., Anen, C., Camerer, C.F., Quartz, S.R., Montague, R.P. . (2005). Getting to know you: Reputation and trust in a two-person economic exchange. *Science, 308*, 78-83.
Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., et al. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *J. Neuroscience, 25*(49), 11489-11493.
Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature, 435*, 673-676.
Kraepelin, E. (1907). Clinical Psychiatry: A Textbook for Students and Physicians (Seventh German Edition ed.). New York: The Macmillan Company.
Krueger, F., McCabe, K., Moll, J., Kriegeskorte, N., Zahn, R., Strenziok, M., et al. (2007). Neural correlates of trust. *PNAS, 104*(50), 20084-20089.
Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). International Affective Picture System (IAPS): Technical Manual and Affective Ratings. Gainesville, FL: National Institute of Mental Health Center for the Study of Emotion and Attention.
Luck, S. J., & Gold, J. M. (2008). The Translation of Cognitive Paradigms for Patient Research. *Schizophrenia Bulletin, 34*(4), 629–644.
Lukoff, D., Nuechterlien, K., & Ventura, J. (1986). Manual for the Expanded Brief Psychiatric Rating Scale. *Schizophrenia Bulletin, 13*(261-276).
MacDonald, A. W., III, Becker, T. M., & Carter, C. S. (2006). Functional magnetic resonance imaging study of cognitive control in the healthy relatives of schizophrenia patients. *Biological Psychiatry, 60*, 1241-1249.
MacDonald, A. W., III, & Carter, C. (2003). Event-related fMRI study of context processing in dorsolateral prefrontal cortex of patients with schizophrenia. *Journal of Abnormal Psychology, 112*(4), 689-697.

MacDonald, A. W., III, & Carter, C. S. (2002). Cognitive experimental approaches to investigating impaired cognition in schizophrenia: A paradigm shift. *Journal of Clinical & Experimental Neuropsychology, 24*, 873-882.

MacDonald, A. W., III, Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288*, 1835-1838.

MacDonald, A. W., III, Pogue-Geile, M. F., Johnson, M. K., & Carter, C. S. (2003). A specific deficit in context processing in the unaffected siblings of patients with schizophrenia. *Archives of General Psychiatry, 60*, 57-65.

MacDonald, A. W., III, Porter, J. N., Johnson, M. K., & Krueger, R. F. (2008). Imaging experience's impact on the brain: an fMRI study of trust in identical twins discordant for persecutory ideation, *Presented at the Society for Neuroscience*. Washington, D.C.

MacDonald, A. W., III, & Schulz, S. C. (2009). What We Know: Findings That Every Theory of Schizophrenia Should Explain. *Schizophrenia Bulletin, 35*(3), 493-508.

Macrae, C. N., Moran, J. M., Heatherton, T. F., Banrield, J. F., & Kelley, W. M. (2004). Medial prefrontal activity predicts memory for self. *Cerebral Cortex, 14*, 647-654.

Madden, G. J., Petry, N., Badger, G., & Bickel, W. K. (1997). Impulsive and self-control choices opiod-dependent subjects and non-drug using controls: drug and monetary rewards *Experimental and Clinical Psychopharmacology, 5*, 256-262.

McCabe, K., Houser, D., Ryan, L., Smith, V., & Trouard, T. (2001). A functional imaging study of cooperation in two-person reciprocal exchange. *PNAS, 98*(20), 11832-11835.

McCrae, R. R., & Paul T. Costa, J. (1987). Validation of the Five-Factor Model of Personality Across Instruments and Observers. *Journal of Personality and Social Psychology, 52*(1), 81-90.

Menon, M., Pomarol-Clotet, E., McKenna, P., & McCarthy, R. (2006). Probabilistic reasoning in schizophrenia: a comparison of the performance of deluded and nondeluded schizophrenic patients and exploration of possible cognitive underpinnings. *Cognit Neuropsychiatry, 11*(6), 521-536.

Mirowsky, J., & Ross, C. E. (1983). Paranoia and the structure of powerlessness. *American Sociological Review, 48*(228-239).

Mitchell, J. P., & Banaji, M. (2006). Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. *Neuron, 50*, 655-663.

Mitchell, J. P., Banaji, M. R., & Macrae, C. N. (2005). General and specific contributions of the medial prefrontal cortex to knowledge about mental states. *Neuroimage, 28*, 757–762.

Mitchell, J. P., Banaji, M. R., & Macrae, C. N. (2005). The link between social cognition and self-referential thought in the medial prefrontal cortex. *J. .Cogn. Neurosci, 17*, 1306-1315.

Mitchell, J. P., Heatherton, T. F., & Macrae, C. N. (2002). Distinct neural systems subserve person and object knowledge. *Proc. Natl Acad. Sci. , 99*, 15238–15243

Ndetei, D. M., & Vadher, A. (1984). Frequency and clinical significance of delusions across cultures. *Acta Psychiatr Scand 70*(1), 73-76.

North, A. S., Russell, A. J., & Gudjonsson, G. H. (2008). High functioning autism spectrum disorders: An investigation of psychological vulnerabilities during interrogative interview. *The Journal of Forensic Psychiatry & Psychology, 19*(3), 323-334.
Ochsner, K. N., Beer, J. S., Robertson, E. R., Cooper, J. C., Gabrieli, J. D. E., Kihsltrom, J. F., et al. (2005). The neural correlates of direct and reflected self-knowledge. *Neuroimage, 28*, 797 – 814.
Ochsner, K. N., Knierim, K., Ludlow, D. H., Hanelin, J., Ramachandran, T., Glover, G., et al. (2004). Reflecting upon Feelings: An fMRI Study of Neural Systems Supporting the Attribution of Emotion to Self and Other. *Journal of Cognitive Neuroscience, 16*(10), 1746-1772.
Overall, J., & Gorham, D. (1962). The brief psychiatric rating scale. *Psychological Reports, 10*, 799-812.
Owen, R. R., Fischer, E. P., Booth, B. M., & Cuffel, B. J. (1996). Medication noncompliance and substance abuse among patients with schizophrenia. *Psychiatric Services, 47*(8), 853-858.
Patrick, C. J., Curtin, J. J., & Tellegen, A. (2002). Development and validation of a brief form of the Multidimensional Personality Questionnaire. *Psychological Assessment, 14*(2), 150-163.
Paulus, M. P., Rogalsky, C., Simmons, A., Feinstein, J. S., & Stein, M. B. (2003). Increased activation of the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *NeuroImage, 19*, 1439-1448.
Pezze, M. A., & Feldon, J. (2004). Mesolimbic dopaminergic pathways in fear conditioning. *Progress in Neurobiology, 74*, 301–320.
Pinkham, A. E., Hopfinger, J. B., Pelfrey, K. A., Piven, J., & Penn, D. L. (2008). Neural basis for impaired social cognition in schizophrenia and autims spectrum disorders. *Schizophrenia Research, 99*, 164-175.
Pinkham, A. E., Hopfinger, J. B., Ruparel, K., & Penn, D. L. (2008). An Investigation of the Relationship Between Activation of a Social Cognitive Neural Network and Social Functioning. *Schizophrenia Bulletin, 34*(4), 688–697.
Poulton, R., Caspi, A., Moffitt, T. E., Cannon, M., Murray, R., & Harrington, H. (2000). Children's Self-Reported Psychotic Symptoms and Adult Schizophreniform Disorder: A 15-Year Longitudinal Study. *Arch Gen Psychiatry, 57*, 1053-1058.
Poundstone, W. (1992). *Prisoner's Dilemma* New York, NY: Doubleday.
Premack, D. W., W. (1978). Does the chimpanzee have a 'theory of mind'? *Behavioral and Brain Sciences, 4*, 515-526.
Raine, A. (1991). The SPQ: A scale for the assessment of schizoptypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin, 17*(4), 555-564.
Rotter, J. B. (1967). A new scale for the measurement of interpersonal trust. *Journal of Personality, 35*(4), 651-665.
Saarinen, P. I., Lehtonen, J., & Lonnqvist, J. (1999). Suicide risk in schizophrenia: an analysis of 17 consecutive cases. *Schizophrenia Bulletin, 25*(3), 533-542.
Sanfey, A. (2007). Social Decision-Making: Insights from Game Theory and Neuroscience. *Science, 318*(26), 598-602.

Sanfey, A. G., Rilling, J. K., Aronson, J. A., Nystrom, L. E., & Cohen, J. D. (2003). The neural basis of economic decision-making in the ultimatum game. *Science, 300*, 1755-1758.
Schmitz, T. W., Kawahara-Baccus, T. N., & Johnson, S. C. (2004). Metacognitive evaluation, self-relevance, and the right prefrontal cortex. *Neuroimage, 22*, 941-947.
Schneider, K. (1959). *Clinical Psychopathology*. New York: Grune and Stratton.
Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry., 59*(Suppl 20), 22-33.
Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*(3), 143-155.
Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23*(s1), 208-219.
Stompe, T., Friedman, A., Ortwein, G., Strobl, R., Chaudhry, H., Najam, N., et al. (1993). Comparisons of delusions among schizophrenics in Austria and Pakistan. *Psychopathology, 32*(5), 225-234.
Stompe, T., Ortwein-Swoboda, G., Ritter, K., Schanda, H., & Friedmann, A. (2002). Are we witnessing the disappearance of catatonic schizophrenia? *Comprehensive Psychiatry, 43*(167-174).
Tellegen, A., Ben-Porath, Y., McNulty, J. L., Arbisi, P. A., Graham, J. R., & Kaemmer, B. (2003). *The MMPI-2 Restructured Clinical (RC) Scales: Development, Validation, and Interpretation*. Minneapolis, MN: University of Minnesota Press.
Tellegen, A., & Waller, N. G. (2008). Exploring Personality Through Test Construction: Development of the Multidimensional Personality Questionnaire. In G. J. Boyle, G. Matthews & D. H. Saklofske (Eds.), *Handbook of personality theory and testing: Vol. II. Personality measurement and assessment* (pp. 261-292). London: Sage.
The-Psychological-Corporation. (2001). Wechsler Test of Adult Reading. San Antonio, TX: Harcourt Assessment.
Thesen, S., Heid, O., Mueller, E., & Schad, L. R. (2000). Prospetive acquisition correction for head motion with image-based tracking foe real-time fMRI. *Magnetic Resonance in Medicine, 44*, 457-200.
Tomlin, D., Kayali, M. A., King-Casas, B., Cedric, A., Camerer, C. F., Quartz, S. R., et al. (2006). Agent-specifc responses in the cingulate cortex during economic exchanges. *Science, 312*, 1047-1050.
Walter, H., Adenzato, M., Ciaramidaro, A., Enrici, I., Pia, L., & Bara, B. G. (2004). Understanding Intentions in Social Interaction: The Role of the Anterior Paracingulate Cortex. *Journal of Cognitive Neuroscience, 16*(10), 1854-1863.
Williams, L. M., Das, P., Harris, A. W. F., Liddell, B. B., Brammer, M. J., Olivieri, G., et al. (2004a). Dysregulation of Arousal and Amygdala-Prefrontal Systems in Paranoid Schizophrenia. *Am J Psychiatry, 161*(13).

Williams, L. M., Das, P., Harris, A. W. F., Liddell, B. B., Brammer, M. J., Olivieri, G., et al. (2004b). Dysregulation of Arousal and Amygdala-Prefrontal Systems in Paranoid Schizophrenia. *American Journal Psychiatry, 161*, 480–489.

Williams, L. M., Dasa, P., Liddell, B. J., Olivieria, G., Peduto, A. S., Davide, A. S., et al. (2007). Fronto-limbic and autonomic disjunctions to negative emotion distinguish schizophrenia subtypes. *Psychiatry Research Neuroimaging, 155*, 29-44.

Wilson, J., & Enoch, M. (1967). Estimation of drug rejection by schizophrenic in-patients, with analysis ofclinical factors. *BritishJournal ofPsychiatry, 113*(209-211).

Winston, J. S., Strange, B. A., O'Doherty, J., & Dolan, R. J. (2002). Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nature Neuroscience, 5*(3), 277-283.

Zysset, S., Huber, O., Fersti, H., & von Cramon, D. Y. (2002). The anterior frontomedian cortex and evaluative judgment: An fMRI study *Neuroimage, 15*, 983-991.

Appendix 1: Historical Descriptions of Schizophrenia Symptoms and Their Corresponding DSM-IV-TR Subtype

Appendix Table 1.1 *History of Schizophrenia Subtypes*

	Negative	Disorganized	Positive
Emil Kraepelin (1856-1929) *Lehrbruck der Psychiatrie* (1907)	Identified disturbances in the emotional field as a characteristic and fundamental symptom of schizophrenia. Described negative symptoms as lack of affection for others the patient previously cared about, and a lack of pleasure in previous interests and employment.	Identified cognitive problems as a symptom in schizophrenia including attention and disturbances in train of thought. Categorized these patients as Hebephrenic, coming from the name Hebe, the Greek goddess of youth, in reference to the typical age of onset in puberty (Athanasiadis, 1997).	Described psychosis as hallucinations, defective judgment, and delusions; the former of which he postulated lead to the latter. Categorized these patients as paranoid, a term still used to describe patients with prominent positive symptoms, although not necessarily persecuted.
Eugen Bleuler (1856-1929) *Dementia Praecox or the Group of Schizophrenia* (1950)	Describe Altered Simple Functions as areas in which the schizophrenia patient is impaired or lacking a skill in some way. Described patients lacking Affectivity "images of indifference… They lack not	Described Associations (also as one of the Simple Functions) in healthy people as "threads that successfully link the thoughts in a logical manner". Described that in schizophrenic thinking a single or group of threads become interrupted	Considered psychosis a type of Compound Function, named as such because he believed that it was a combination of the impairment in associations and affectivity which gave rise to them

	only the ability to react to the world, but also to act upon it. They show indifference to "friends and relations, to vocation or enjoyment, to duties or rights, to good fortune of bad".	and "two ideas, fortuitously encountered, are combined into one thought; the logical form being determined by incidental circumstances".	
Kurt Schneider (1887-1967) *Clinical Psychopathology* (1959)			Differed from both Kraepelin and Bleuler in that he believed that certain symptoms were pathognomonic of schizophrenia. Schneiderian First Rank Symptoms (FRS) include auditory hallucinations of voices conversing or commenting and the belief that one's thoughts are being broadcasted out loud, inserted, or withdrawn.
DSM-IV-TR Subtype	Residual	Disorganized	Paranoid
	Applied when there has been at least one episode of Schizophrenia, but the current clinical picture is without prominent positive psychotic	Applied when disorganized speech, disorganized behavior, and flat or inappropriate affect are prominent.	Applied when delusions or hallucinations are prominent.

	symptoms, such as delusions, hallucinations, disorganized speech or behavior. This is the subtype that is most closely related to negative symptoms.	

Appendix 2: Changes in the Diagnostic Criteria of Schizophrenia over the Past 40 Years.

Appendix Table 2.1 *Schizophrenia Diagnostic Criteria Changes*

	Positive	Disorganized	Negative	Catatonic*
Feigner Criteria (1972)	One required		Not included	
DSM-III (1980)	One required			
DSM-III-R (1987)	Two required; one if Schneiderian FRS			
DSM-IV-TR (2000)				
	Mood	**Duration**	**Rule-outs**	**Misc**
Feigner Criteria (1972)	Rule out	6 months	Not included	One of the following: single, premorbid maladjustment or family history of schizophrenia
DSM-III (1980)	Rule out IF: proceeded psychosis or not brief relative to psychosis		Not due to MR or “Organic Mental Disorder”	Prodromal and residual phases required Onset before age of 45
DSM-III-R (1987)	Rule of IF: presence of schizoaffective or mood disorder with psychotic features	1 week active phase; 6 months of impairment	Not due to organic factor If Autism is present delusions or hallu-cinations are prominent	Prodromal or residual phases not required
DSM-IV-TR (2000)		1 month of active phase unless treated	Not due to a general medical	

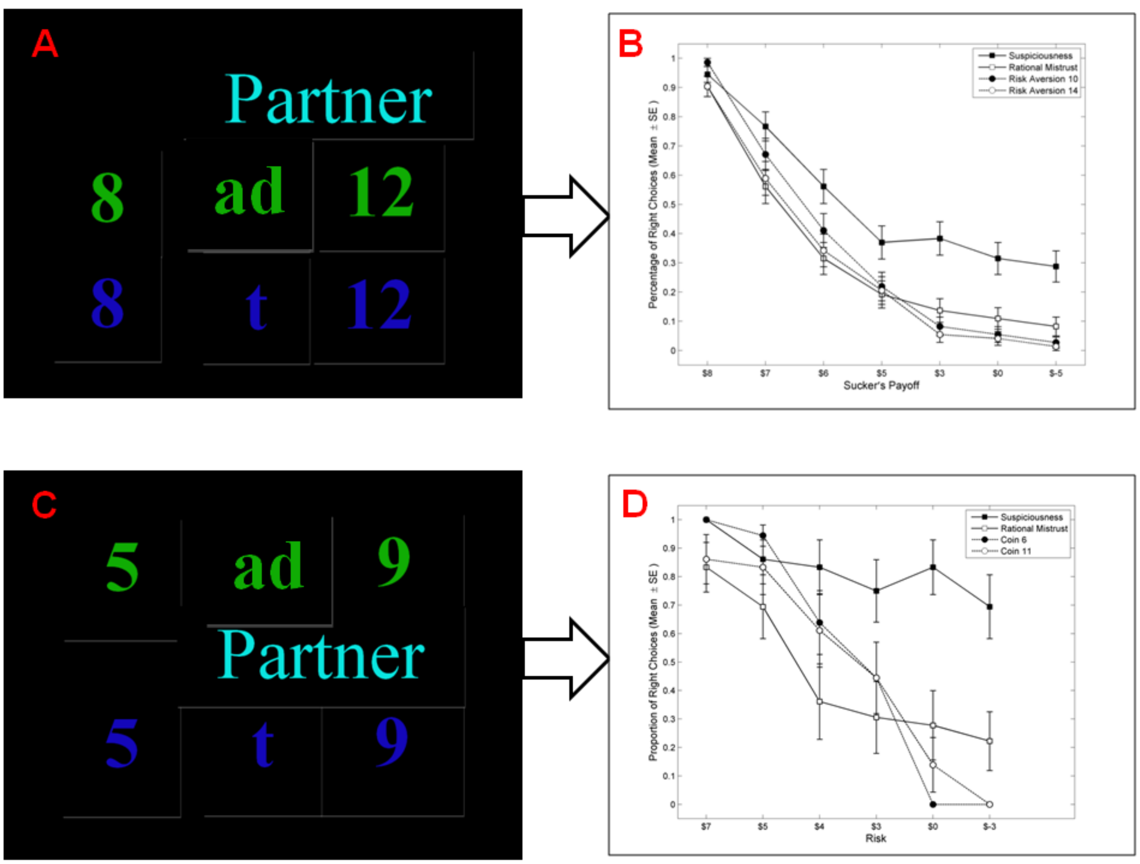
			condition or substance; If Autism is present, delusions or hallucinations must be prominent	

Note: A discussion of schizophrenia symptomatology would not be complete without the discussion of catatonia, a subtype and symptoms that has become increasingly rare, perhaps due to improvement in treatment with neuroleptic medication (Carpenter, J.J., Carpenter, & Strauss, 1976; T. Stompe, Ortwein-Swoboda, Ritter, Schanda, & Friedmann, 2002). Catatonia was considered a main symptom by both Kraepelin and Bleuler. The DSM-IV-TR included a Catatonic Subtype that is described as “marked psychomotor disturbance that may involve motoric immobility, excessive motor activity, extreme negativism, mutism, peculiarities of voluntary movement, echolalia, or echopraxia”(American-Psychiatric-Association, 2000).

Appendix 3: Translating the Minnesota Trust Game into a Sample of Individuals with Schizophrenia

The current version of the Minnesota Trust Game (MTG, verson 4) is the result of four iterations of data collection and task modifications. The original versions of the task relied on participants' ability to memorize the meaning of the locations and colors of the numbers on the screen (Figures 1A and 2A). For example, part of the instructions for versions 1, 2 and 3 read, "The top row of numbers in green represent your winnings, while the bottom row of numbers in blue represent the other player's potential winnings."

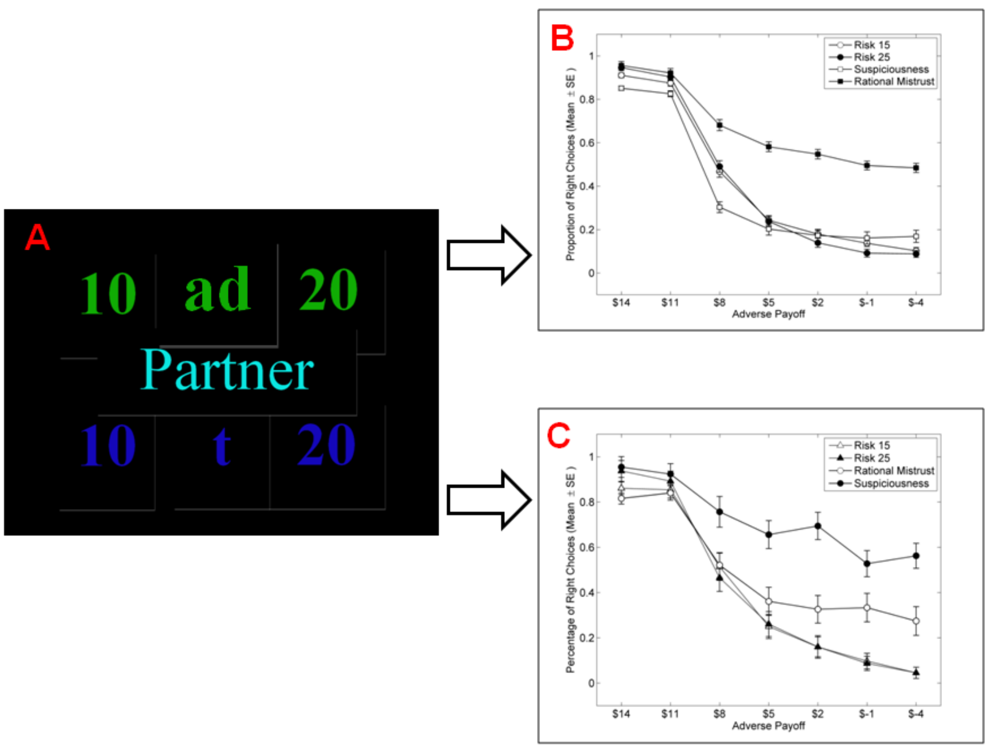
Appendix Figure 3.1 *Minnesota Trust Game Versions 1 and 2*



Note: Image A is a screen shot from version 1 of the MTG and image B is the line graph from the decision-making results in a sample of undergraduate students run in small group settings (M.K. Johnson, Rustichini, et al., 2009). Image C is a screen shot from version 2 of the MTG and image D is the line graph from the decision-making results in a small sample of community participants (n=12) (M. K. Johnson, Walter, Carter, & MacDonald, 2007). All numbers in green represent the participant's potential winnings and the numbers in blue represent the partner's potential winnings. The *ad* stands for *adverse payoff*, which would appear to the participant as a number between -$5 and $8 in version 1.0, and -$3 to $7 in version 2.0. The *t* stands for *temptation*, which would appear to the participant as either $10 or $14 in version 1.0, and $6 or $9 in version 2.0.

Additionally, participants needed to maintain that the left button-press resulted in *assured payoff* for both players while the outcome of the right button-press was conditional upon the choice of the 'partner'. The hypothesized results were obtained in all of the control samples (Appendix Figures 3.1 and 3.2) and have improved over parameterizations of the task.

Appendix Figure 3.2 *Minnesota Trust Game Version 3*

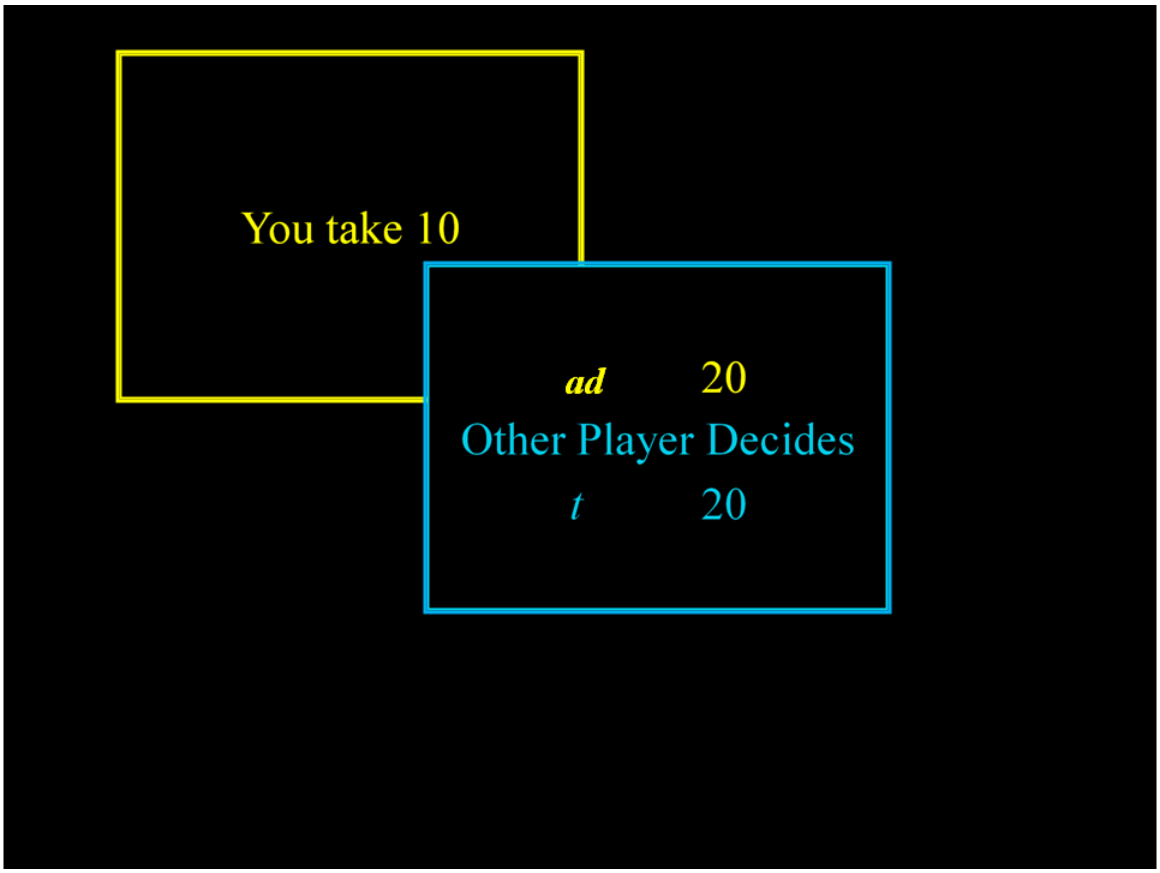


Note: Image A is a screen shot from version 4 of the MTG and images B and C are line graphs from the decision-making results in a sample of undergraduate students (n=243) (M.K. Johnson, Duquette, et al., 2009) and monozygotic twins (n=46) (M.K. Johnson & MacDonald III, 2009; MacDonald, et al., 2008). All numbers in green represent the participant's potential winnings and the numbers in blue represent the partner's potential winnings. The *ad* stands for *adverse payoff*, which would appear to the participant as a number between -$10 and $20. The *t* stands for *temptation*, which would appear to the participant as either $15 or $25.

In contrast to control samples, results from a sample of patients collected at the VA indicated poor task-comprehension. First, patients were not sensitive to the built-in validity condition (e.g., choosing the *assurred payoff* in multiple trials when either outcome in the right columns resulted in a greater payoff) . Second, many patients showed inconsistent decision-making patterns. For example, choosing 'right' when the *adverse payoff* was -$5 after having chosen *assured payoff* when the *adverse payoff* was $-4, -$3, -$2, etc. Control participants occassionally displayed such response patterns, but a qualitative evaluation of individual patient's data showed that 'invalid' and inconsistent response pattern were more common in patients. Based on the association of schizophrenia and executive dysfunction, particularly working memory, we interpreted these problematic response patterns as a result of the task's high cogntivie load. Consequently, we realized the need for modifying the MTG to decrease the tasks's cognitive demand.

Based on the idea of token economies in behavioral modification programs in schizophrenia, we decided a physical representation of the choices would help patients maintain relevant information. The *assured payoff* ('You take 10') was made into one card and the conditonal outcomes (Other Player or Coin-flip decides) were made into a separate card (Appendix Figure 3.2).

Appendix Figure 3.3 *Minnesota Trust Game Version 4*



Note: Pictured is version 4.0 of the Minnesota Trust Game. The 'card' with the yellow outline represents the *assured payoff*. All values in yellow represent the participant's potential winnings. The card with the blue outline represents the conditional outcome. In this example the other player would determine the outcome. All numbers in blue represent the other player's potential winnings. The *ad* stands for *adverse payoff*, which would appear to the participant as a number between -$10 and $20. The *t* stands for *temptation,* which would appear to the participant as either $15 or $25.

Patients were trained using a stack of laminated index-sized cards with dollar signs next to the *adverse payoff* that are not included in the neuroimaging procedure.

Patients then practiced a computerized version of the game using the ‘up’ and ‘down’ arrow keys for the ‘top’ and ‘bottom’ cards. As a result, the ‘top’ and ‘bottom’ button press became automatic before entering the scanner. Replacing the matrix of numbers with cards eliminates the need for patients to maintain a distinction between the left and right columns and provides a more intuitive context for the numbers. While the inclusion of more verbage may increase eye movement it conveys the meaning of the cards without heavily relying on color-coding or location.

Finally, the positive connotation of the word ‘partner’ may have uncessearily imposed strategies on certain participants. In previous versions, multiple participants interpreted their ‘partner’ as a ‘team’ member and played the game to maximize total winnings across the participant and the partner. For many participants it was a source of confusion, “Am I playing against this person or with them?” The response to such questions by the experimenter was, “Make the decision that seems best to you”. While these are valid (and understandable) strategies and questions, we opted for the more neutral phrase, ‘other player’ to reduce the potential for social desireability biases.

The dollar values of the task parameters did not change from versions 3 to 4, allowing for us to make general comparisons between samples. Based on the results from the sample of 32 patients shown in Chapter, changes made appear to have reduced the cognitive load of the task and greatly improved patient comprehension.

Appendix 4: The Suspiciousness Item from the Brief Psychiatric Rating Scale - Expanded Version (Lukoff, et al., 1986; Overall & Gorham, 1962)

Suspiciousness
Expressed or apparent belief that other persons have acted maliciously or with discriminatory intent. Include persecution by supernatural or other non-human agencies (e.g., the devil). Note: ratings of 3 or above should also be rated under Unusual Thought Content.

2 Very mild Seems on guard. Reluctant to respond to some `personal' questions. Reports being overly self-conscious in public.

3 Mild Describes incidents in which others have harmed or wanted to harm him/her that sound plausible. Individual feels as if others are watching, laughing or criticizing him/her in public, but this occurs only occasionally or rarely. Little or no preoccupation.

4 Moderate Says other persons are talking about him/her maliciously, have negative intentions or may harm him/her. Beyond the likelihood of plausibility, but not delusional. Incidents of suspected persecution occur occasionally (less than once per week) with some preoccupation.

5 Moderately Severe Same as 4, but incidents occur frequently, such as more than once per week. Individual is moderately preoccupied with ideas of persecution OR individual reports persecutory delusions expressed with much doubt (e.g., partial delusion).

6 Severe Delusional - speaks of Mafia plots, the FBI or others poisoning his/her food, persecution by supernatural forces.

7 Extremely Severe Same as 6, but the beliefs are bizarre or more preoccupying. Individual tends to disclose or act on persecutory delusions.

"Do you ever feel uncomfortable in public? Does it seem as though others are watching you? Are you concerned about anyone's intentions toward you? Is anyone going out of their way to give you a hard time, or trying to hurt you? Do you feel in any danger?"

[If individual reports any persecutory ideas/delusions, ask the following]:
"How often have you been concerned

Appendix 5: Characterization of Second Mover Decisions

The Second Mover game is included in the Minnesota Trust Game (MTG) so that for a number of reasons. First, the field of behavioral economics discourages the practice of deception any study using a decision-making paradigm in order protect the integrity of the field from the perspective of participants. Since participants playing the MTG are paid for their choices, also common practice in the field of behavioral economics, the experimenter needs the Second Mover choices in order to determine payment for First Mover choices. Second, though we have not tested this empirically, it stands to reason that playing the role of the Second Mover before first would provide context for the First Mover choices. Anecdotally, it has been my experience that this context facilitates comprehension of the logistics of the task and brings to life the financial (and emotional) consequences of the participant's choices. Finally, results from the Second Mover game also provide an opportunity to evaluate participant task comprehension.

Based on the task design and results from previous samples we predicted that patient would be less willing to betray the other player in Spitefulness condition than the Selfishness condition which would manifest as a main effect of *temptation*. We also predicted that the adverse payoff would have stronger impact on behavior in the Selfishness condition than in Spitefulness, which would manifest as a *temptation* by *adverse payoff* interaction.

Reaction times and response rates for the Second Mover game are presented in Appendix Table 5.1. Participants responded to each trial in the Second Mover game. The average reaction time across conditions was 3122.52 MS (SD=340.33). The level of the *temptation* significantly modulated reaction time such that participant were slower during decisions in the Selfishness condition (*t*(30)=3.45, p<.002). Choice was coded such that '0' was equal to a cooperation or *the mutual reward* and '1' was equal to a betrayal or selecting the *temptation*. Overall, participants selected the *temptation* over the cooperative choice 22.13% (SD=3.2%).

Appendix Table 5.1 *Reaction Time and Choices from MTG Second Mover Game*

	Reaction Time	Proportion of Uncooperative Choices
Spitefulness	2726.46 (292.09)	.03 (.01)
Selfishness	3518.58 (415.59)	.42 (.06)

A repeated measures logistic regression of the task manipulations*, temptation (t)* and *adverse payoff (ad)* on choice as a second mover resulted in main effects of *temptation* and *adverse payoff* (Appendix Table 5.2). However, the two-way interaction of *t*ad* was not significant suggesting that the *adverse payoff* had a similar effect across the Spitefulness and Selfishness conditions.

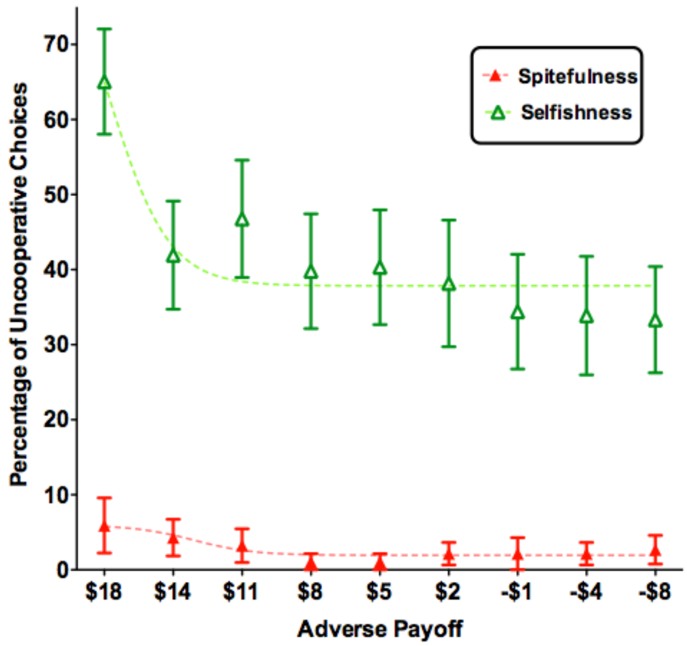
Appendix Table 5.2 *Repeated Measures Logistic Regression of MTG Second Mover Choices*

Variable	**Coefficient**	**SE**	**95 % CI**	***p***
All Trials				
Constant	0.908	0.32	0.28 to 1.535	.005
Temptation	-3.357	0.753	-4.834 to -1.88	.000
Adverse Payoff	-0.172	0.05	-0.269 to -0.075	.001
Temptation by Adverse Payoff	0.097	0.134	-0.166 to 0.359	.471

The absence of the *t*ad* finding is reflected in the line graph of participant's choices shown in Appendix Figure 5.1. Aside from a spike in uncooperative choices at *ad*= $20, 18 and $16 in the Selfishness condition, the lines are largely parallel. Though *ad* showed a significant association with choice across conditions (OR = .534, 95% CI

[.382, .862]; 0 = *ad*>$9 and 1 = *ad*<$10) the effect of *t* on choice (OR = .053, 95% CI [.019, .148]; 0 = *t=$15* and 1 = *t=$25*)) appeared stronger based on their odds ratios.

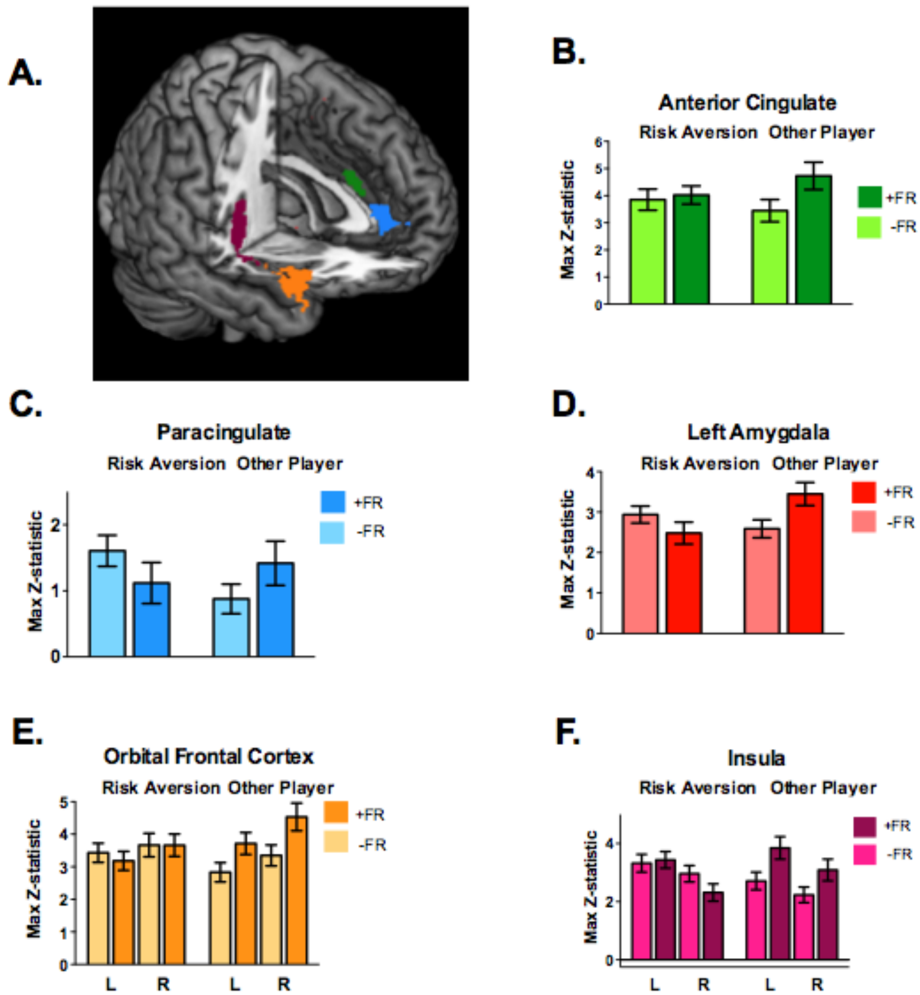
Appendix Figure 5.1 *Second Mover Choices by Condition*



The pattern of effects in patients is consistent with our results in twins (M.K. Johnson & MacDonald III, 2009). Similar to patients, twins were less likely to betray as when *ad* < $10 (OR = .368, 95% CI [.261, .514]; 0 = *ad* > $9 and 1 = *ad* < $10). Both groups were willing to compromise their own winnings in order to avoid causing the other player a financial loss. Also like patients, twins were less likely to betray in the Spitefulness than Selfishness condition ((OR = .053, 95% CI [.024, .114]; 0 = *t=$15* and 1 = *t=$25*)). Both groups were extremely unlikely to take a financial loss in order to cause a financial loss for the other player. Interestingly, the neither group showed the *t* by *ad* interaction that we found previously in a sample of undergraduate students. In summary, the results from the Second Mover data are additional support that this sample of patient's behavior on the MTG paralleled that of community controls.

Appendix 6: Maximum Z-statistics from the Other Player Greater than Risk Aversion Contrast (Decision-agent by Financial Risk)

Appendix Figure 6.1. *Decision-Agent by Financial Risk Contrast (Max Z-statistics)*



Note: A. Brain image of areas where the Other Player financial risk trials showed greater activation than the Other Player no risk trials controlling for Risk Aversion. B-F. Bar graphs showing financial risk (+FR) and no financial risk (-FR) for the Risk Aversion and Other Player conditions for each area identified in the group *decision-agent* by *financial risk* contrast. The y-axis represents the mean unthresholded max Z-statistics extracted from individual subject contrast maps.

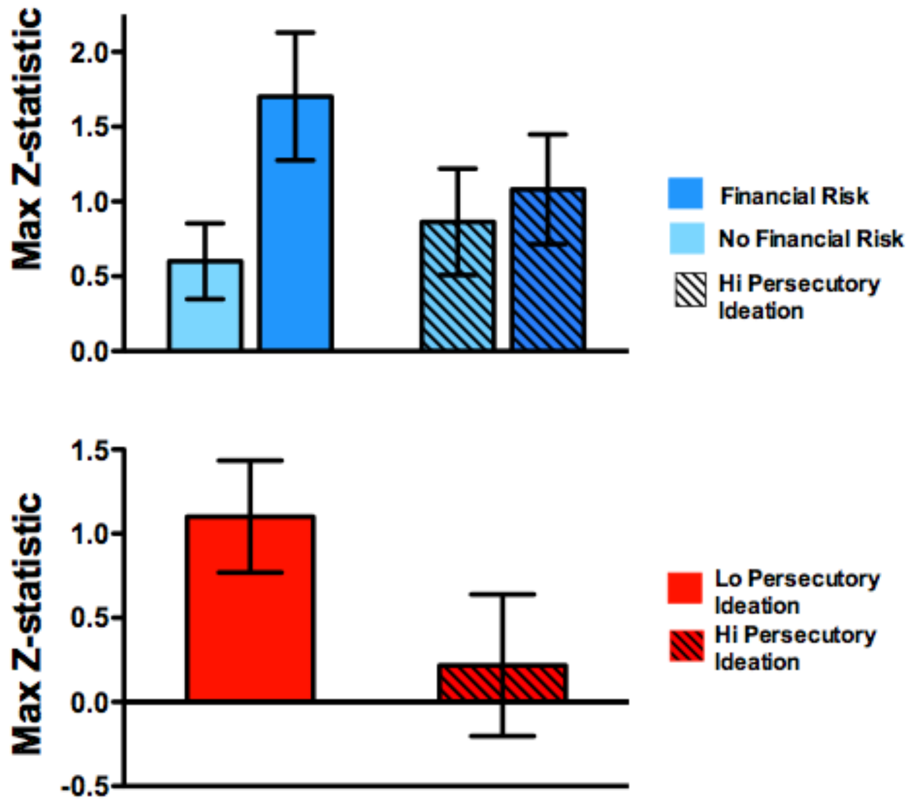
Appendix 7: Effect of Financial Risk in Suspiciousness Condition by Persecutory Ideation Group in the Paracingulate Cortex

Persecutory Ideation was associated with less trusting behavior in the Suspiciousness condition but not Rational Mistrust and Risk Aversion. In order to display the differences in behavior resulting from Persecutory Ideation we created Persecutory Ideation groups using a median split. Though the 4-way interaction of *Decision-agent*temptation*adverse Payoff*Persecutory Ideation* did not reach significance (ß= .001, p=.064), Figure 12 (Chapter 4) suggested that the differences associated with Persecutory Ideation became more pronounced at higher levels of financial risk. As a result we were curious to explore if using a median split in the contrast of financial risk levels in the Suspiciousness condition would improve our sensitivity to differences in neural activity associated with Persecutory Ideation.

In a sample of sample of monozygotic twins (n=46) we found that the difference in twin pair's *Alienation* (Patrick, et al., 2002) T-scores was positively correlated with the difference between their parameter estimates in the paracingulate (PcC) activation found in the Suspiciousness greater than Rational Mistrust contrast (*t*financial risk*) (MacDonald, et al., 2008). As a result, we examined the relationship between Persecutory Ideation group and activation in the PcC in the contrast of financial risk in the Suspiciousness condition.

We found that patients with higher levels of Persecutory Ideation showed less of a difference between the two levels of financial risk than patients with low levels of persecutory beliefs in the paracingulate ($t(31)=1.65$, P=.055, one-tailed) (Figure 6).

Appendix Figure 6.2. *The Effect of Financial Risk by Persecutory Ideation Group in Suspiciousness Condition: Paracingulate*



Note: **Top Figure**: Bar graph showing the effect of financial risk in the Suspiciousness condition by Persecutory Ideation group. The y-axis represents the mean unthresholded max Z-statistics extracted from individual subject contrast maps **Bottom Figure**: Bar graph showing the difference in max Z-statistics between financial risk and no financial risk in the Suspiciousness condition.

This finding is in the opposite direction of high Persecutory Ideation twin pairs who showed increased activity in the PcC compared their low Persecutory Ideation twin. The increased PcC in high Persecutory Ideation twins was interpreted as increased processing of the other player's disincentive in the financial risk compared to the no financial risk condition. The current finding suggested that patients with high Persecutory Ideation are less sensitive to financial risk though the differences in absolute activation levels do not appear significantly different.

Appendix References

Adolphs, R. (2001). The neurobiology of social cognition. *Curr Opin Neurobiol, 11*, 231-239.

Adolphs, R., Tranel, D., & Damasio, A.R. (1998). The human amygdala in social judgement. *Nature, 393*, 470-474.

Allardyce, J., Gaebel, W., Zielasek, J., & van Os, J. (2007). Deconstructing Psychosis Conference February 2006: The Validity of Schizophrenia and Alternative Approaches to the Classification of Psychosis. . *Schizophr Bull, 33*(4), 863–867.

American-Psychiatric-Association (Ed.). (2000). *Diagnostic and Statistical Manual of Mental Disorders* (Fourth, Text Revision ed.). Washington, D.C.: American Psychiatric Association.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience, 7*, 268-277.

Andreasen, N. C., Arndt, S., Alliger, R., Miller, D., & Flaum, M. (1995). Symptoms of schizophrenia: Methods, meanings, and mechanisms. *Arch Gen Psychiatry, 52*, 341-351.

Andreasen, N. C., & Olsen, S. (1982). Negative v Positive Schizophrenia. *Arch Gen Psychiatry, 39*, 789-794.

Appelbaum, P. S., Robbins, P. C., & Roth, L. H. (1999). Dimensional approach to delusions: Comparison across types and diagnoses. *American Journal of Psychiatry, 156*(12), 1938-1943.

Arseneault, L., Moffit, T. E., Caspi, A., Taylor, P. J., & Silva, P. A. (2000). Mental disorders and violence in a total birth cohort. *Archives of General Psychiatry, 57*, 979-986.

Athanasiadis, L. (1997). Greek mythology and medical and psychiatric terminology. *Psychiatric Bulletin, 21*, 781-782.

Barch, D., Carter, C., MacDonald, A., Braver, T., & Cohen, J. (2003). Context processing deficits in schizophrenia: Diagnostic specificity, four-week course, and relationships to clinical symptoms. *Journal of Abnormal Psychology, 112*, 132-143.

Bentall, R. P., Rowse, G., Shryane, N., Kinderman, P., Howard, R., Blackwood, N., et al. (2009). The Cognitive and Affective Structure of Paranoid Delusions A Transdiagnostic Investigation of Patients With Schizophrenia Spectrum Disorders and Depression
. *Arch Gen Psychiatry, 66*(3), 236-247.

Berg, J. (1995). Trust, reciprocity, and social history. *Games and Economic Behavior, 10*, 122-142.

Blackshaw, A. J., Kinderman, P., Hare, D. J., & Hatton, C. (2001). Theory of mind, causal attribution and paranoia in Asperger syndrome. *Autism, 5*(2), 147-163.

Blackwood, N. J., Howard, H.J., Bentall, R.P., Murray, R.M. (2001). Cognitive neuropsychiatric models of persecutory delusions. *American Journal of Psychiatry, 158*, 527-539.

Bleuler, E. (1950). *Dementia praecox or the group of schizophrenias* (T. b. J. Zinkin, Trans.). New York: International Universities Press (Original work published 1911).

Bohnet, I., & Zeckhauser, R. (2004). Trust, risk and betrayal. *Journal of Behavior and Organization, 55*, 467-484.

Bottlender, R., Jager, M., Strauss, A., & Moller, H. J. (2000). Suicidality in bipolar compared to unipolar depressed inpatients. *European Archives of Psychiatry & Clinical Neuroscience., 250*(5), 257-261.

Butcher, J. N. W., C.L. (2000). *Essentials of MMPI-2 and MMPI-A Interpretation* (2 ed.). Minneapolis, MN: University of Minnesota Press.

Carpenter, W. T. (2007). Schizophrenia: Disease, Syndrome, or Dimensions? *Family Process, 46*(2), 199-206.

Carpenter, W. T., Heinrichs, D. W., & Wagman, A. M. (1988). Deficit and nondeficit forms of schizophrenia: The concept. *American Journal of Psychiatry, 145*(5), 578-583.

Carpenter, W. T., J.J., B., Carpenter, C. L., & Strauss, J. S. (1976). Another View of Schizophrenia Subtypes: a Report from the International Pilot Study of Schizophrenia. *Arch Gen Psychiatry, 33*, 508-516.

Chiu, P. H., Kayali, A., Kishida, K. T., Tomlin, D., Klinger, L. G., Klinger, M. R., et al. (2008). Self Responses along Cingulate Cortex Reveal Quantitative Neural Phenotype for High-Functioning Autism. *Neuron, 57*, 463-473.

Cohen, J. D., Barch, D. M., Carter, C. S., & Servan-Schreiber, D. (1999). Context-processing deficits in schizophrenia: Converging evidence from three theoretically motivated cognitive tasks. *Journal of Abnormal Psychology, 108*(1), 120-133.

Cohen, J. D., & Servan-Schreiber, D. (1992). Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychological Review, 99*(1), 45-77.

Cook, W., & Medley, D. (1954). Proposed hostility and parisaic-virtue scales for the MMPI. *Jounral of Applied Psychology, 38*, 414-418.

Corcoran, R., Cummins, S., Rowse, G., Moore, E., Blackwood, N., Howard, R., et al. (2006). Reasoning under uncertainty: heuristic judgments in patients with persecutory delusions or depression. *Psychol Med, 36*(8), 1109-1118.

Corcoran, R., Mercer, G., & Frith, C. D. (1995). Schizophrenia, symptomatology and social inference: Investigation 'theory of mind' in people with schizophrenia. *Schizophrenia Research, 17*, 5-13.

Costa, P. T., Zonderman, A. B., McCrae, R. R., & Williams, R. B., Jr. (1986). Cynicism and Paranoid Alienation in the Cook and Medley HO Scale. *Psychosomatic Medicine, 48*(3/4), 283-285.

D'Argembeau, A., Collette, F., Van der Linden, M., Laureys, S., Del Fiore, G., Degueldre, C., et al. (2005). Self-referential reflective activity and its relationship with rest: a PET study. *Neuroimage, 25*, 616-624.

David, N., Bewernick, B. H., Cohen, M. X., Newen, A., Lux, S., Fink, G. R., et al. (2006). Neural Representations of Self versus Other: Visual–Spatial Perspective Taking and Agency in a Virtual Ball-tossing Game. *Journal of Cognitive Neuroscience, 18*(6), 898–910.

Delgado, M. R., Frank, R.H., & Phelps, E.A. . (2005). Perceptions of moral character modulate the neural system of reward during a trust game. *Nature Neuroscience, 8*(11), 1611-1618.

Dikeos, D., Wickham, H., McDonald, C., WALSHE, M., SIGMUNDSSON, T., BRAMON, E., et al. (2006). Distribution of symptom dimensions across Kraepelinian divisions. *Br J Psychiatry, 189*, 346-353.

DiLalla, D. L., & Gottesman, I. I. (1995). Normal personality characteristics of identical twins discordant for schizophrenia. *Journal of Abnormal Psychology, 104*(3), 490-499.

Eckel, C. C., & Wilson, R. K. (2004). Is trust a risky decision? *J. of Economic Behavior & Org, 55*(4), 447–465.

Elliott, R., Dolan, R. J., & Frith, C. D. (2000). Dissociable functions in he medial and lateral orbitofrontal cortex: Evidence from human neuroimaging studies. *Cerbral Cortex, 10*, 308-317.

Feighner, J. P., Robins, E., Guze, S. B., Woodrmff, E. A., Winokur, G., & Munoz, R. (1972). Diagnostic Criteria for Use in Psychiatric Research. *Arch Gen Psychiatry, 26*, 57-63.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute.

Freeman, D., Garety, P. A., Bebbington, P. E., Smith, B., Rollinson, R., & Fowler, D. (2005). Psychological investigation of the structure of paranoia in a non-clinical population. *British Journal of Psychiatry, 186*, 427-435.

Freeman, D. G., P.A. (2004). *Paranoia: The Psychology of Persecutory Delusions*. East Sussex: Psychology Press.

Frith, C. D. (2004). Schizophrenia and theory of mind. *Psychological Medicine, 34*, 385-389.

Fuchs, T. (1992). Life events in late paraphrenia and depression. *Psychopathology, 32*, 60-69.

Gallagher, H. L., Jack, A. I., Roepstorff, A., & Frith, C. D. (2002). Imaging the intentional stance in a competitive game. *Neuroimage, 16*, 814-821.

Gold, J. M., Waltz, J. A., Prentice, K. J., Morris, S. E., & Heerey, E. A. (2008). Reward processing in schizophrenia: a deficit in the representation of value. *Schizophr Bull. , 34*(5), 835-847.

Gunnthorsdottir, A., McCabe, K., & Smith, V. (2002). Using the Machiavellianism instrument to predict trustworthiness in a bargaining game. *Journal of Economic Psychology, 23*, 59-66.

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *PNAS, 98*(7), 4259–4264.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience, 2*(10), 685-964.

Han, K., Weed, N. C., Calhoun, R. F., & Butcher, J. N. (2000). Psychometric Charateristics of the MMPI-2 Cook-Medley Hostility Scale. In J. N. Butcher (Ed.), *Basic Sources on the MMPI-2*. Minneapolis: University of Minnesota Press.

Hathaway, S. R., & McKinley, J. C. (1940). A multiphasic personality schedule (Minnesota): I. Construction of the schedule. *Journal of Psychology, 10*, 249-254.

Haut, K. M., Lim, K. O., & MacDonald, A. W. I. (2010). Prefrontal Cortical Changes Following Cognitive Training in Patients with Chronic Schizophrenia: Effects of Practice, Generalization, and Specificity. *Neuropsychopharmacology, 35*, 1850-1859.

Heerey, E. A., Matveeva, T. M., & Gold, J. M. (2011). Imagining the future: degraded representations of future rewards and events in schizophrenia. *J Abnorm Psychol, 120*(2), 483-439.

Hemsley, D., & Garety, P. (1986). Formation and maintenance of delusions: a Bayesian analysis. *Br J Psychiatry, 149*, 51–56.

Heretick, D. M. L. (1981). Gender-specific relationships between trust-suspicion, locus of control and psychological distress. *Journal of Psychology, 108*, 267-274.

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III -- The final common pathway. *Schizophr Bull, 35*(3), 549-562.

Huber, D., Veinante, P., & Stoop, R. (2005). Populations in the Central Amygdala Vasopressin and Oxytocin Excite Distinct Neuronal. *Science, 308* (8), 245-248.

Janssen, I., Hanssen, M., Bak, M., Bijl, R. V. , de Graaf, R., & Vollenberg, W. (2003). Discrimination and delusional ideation. *British Journal of Psychiatry, 182*, 71-76.

Johnson, M. K., Duquette, S., Steen, M., & MacDonald III, A. W. (2009). A Multiple Method Study Explores Personality Traits and Decision-making Biases Associated with Persecution, Cynicism, and Hostility, *Poster presented at the Society for Research in Psychopathology*. Minneapolis, MN.

Johnson, M. K., & MacDonald III, A. W. (2009). Economic decision-making task behavior predicts discordance of persecutory ideation, *Poster presented at the Behavioral Genetics Society*. Minneapolis, MN.

Johnson, M. K., Rustichini, A., & MacDonald, A. W., III. (2009). Suspicious personality predicts behavior in a social decision-making task. *Personality and Individual Differences, 47*, 30–35.

Johnson, M. K., Walter, R., Carter, C. S., & MacDonald, A. W. (2007). Dissociating the Neural Basis of Suspiciousness from Rational Mistrust and Risk Aversion: An fMRI Study of the Minnesota Trust Game, *Poster presented at the 11th Biennial International Congress of Schizophrenia Research*. Colorado Springs, CO.

Johnson, S. C., Baxter, L. C., Wilder, L. S., Pipe, J. G., Heiserman, J. E., & Prigatano, G. P. (2002). Neural correlates of self-reflection. *Brain, 125*, 1808-1814.

Kahneman, D. T., A. (1979). Prospect theory: An analysis of decision under risk. *Econometrica, 47*(2), 263-292.

Kaney, S., & Bentall, R. (1989). Persecutory delusions and attributional style. *British Journal of Medical Psychology, 62*, 191-198.
Kaney, S., Bowen-Jones, K., Dewey, M., & Bentall, R. (1997). Two predictions about paranoid ideation: deluded, depressed and normal participants' subjective frequency and consensus judgments for positive, neutral and negative events. . *Br J Clin Psychol, 36*(3), 349-364.
Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., lnati, S., & T.F., H. (2002). Finding the self: An event-related fMRI study. *Journal of Cognitive Neuroscience, 14*(785-794).
Kerns, J., & Berenbaum, H. (2002). Cognitive impairments associated with formal thought disorder in people with schizophrenia. *Journal of Abnormal Psychology, 111*(2), 211-224.
Kinderman, P., & Bentall, R. P. (1996). A new measure of causal locus: the internal, personal and situational attributions questionnaire *Personality and Individual Differences, 20*(2), 261-264.
Kinderman, P., & Bentall, R. P. (1997). Causal attributions in paranoia and depression: internal, personal, and situational attributions for negative events. *Journal of Abnormal Psychology, 106*(103-107).
King-Casas, B., Sharp, C., Lomax-Bream, L., Lohrenz, T., Fonagy, P., & Montague, P. R. (2008). The Rupture and Repair of Cooperation in Borderline Personality Disorder. *Science, 321*, 806-810.
King-Casas, B., Tomlin, D., Anen, C., Camerer, C.F., Quartz, S.R., Montague, R.P. . (2005). Getting to know you: Reputation and trust in a two-person economic exchange. *Science, 308*, 78-83.
Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., et al. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *J. Neuroscience, 25*(49), 11489-11493.
Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature, 435*, 673-676.
Kraepelin, E. (1907). Clinical Psychiatry: A Textbook for Students and Physicians (Seventh German Edition ed.). New York: The Macmillan Company.
Krueger, F., McCabe, K., Moll, J., Kriegeskorte, N., Zahn, R., Strenziok, M., et al. (2007). Neural correlates of trust. *PNAS, 104*(50), 20084-20089.
Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). International Affective Picture System (IAPS): Technical Manual and Affective Ratings. Gainesville, FL: National Institute of Mental Health Center for the Study of Emotion and Attention.
Luck, S. J., & Gold, J. M. (2008). The Translation of Cognitive Paradigms for Patient Research. *Schizophrenia Bulletin, 34*(4), 629–644.
Lukoff, D., Nuechterlien, K., & Ventura, J. (1986). Manual for the Expanded Brief Psychiatric Rating Scale. *Schizophrenia Bulletin, 13*(261-276).
MacDonald, A. W., III, Becker, T. M., & Carter, C. S. (2006). Functional magnetic resonance imaging study of cognitive control in the healthy relatives of schizophrenia patients. *Biological Psychiatry, 60*, 1241-1249.

MacDonald, A. W., III, & Carter, C. (2003). Event-related fMRI study of context processing in dorsolateral prefrontal cortex of patients with schizophrenia. *Journal of Abnormal Psychology, 112*(4), 689-697.

MacDonald, A. W., III, & Carter, C. S. (2002). Cognitive experimental approaches to investigating impaired cognition in schizophrenia: A paradigm shift. *Journal of Clinical & Experimental Neuropsychology, 24*, 873-882.

MacDonald, A. W., III, Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288*, 1835-1838.

MacDonald, A. W., III, Pogue-Geile, M. F., Johnson, M. K., & Carter, C. S. (2003). A specific deficit in context processing in the unaffected siblings of patients with schizophrenia. *Archives of General Psychiatry, 60*, 57-65.

MacDonald, A. W., III, Porter, J. N., Johnson, M. K., & Krueger, R. F. (2008). Imaging experience's impact on the brain: an fMRI study of trust in identical twins discordant for persecutory ideation, *Presented at the Society for Neuroscience*. Washington, D.C.

MacDonald, A. W., III, & Schulz, S. C. (2009). What We Know: Findings That Every Theory of Schizophrenia Should Explain. *Schizophrenia Bulletin, 35*(3), 493-508.

Macrae, C. N., Moran, J. M., Heatherton, T. F., Banrield, J. F., & Kelley, W. M. (2004). Medial prefrontal activity predicts memory for self. *Cerebral Cortex, 14*, 647-654.

Madden, G. J., Petry, N., Badger, G., & Bickel, W. K. (1997). Impulsive and self-control choices opiod-dependent subjects and non-drug using controls: drug and monetary rewards *Experimental and Clinical Psychopharmacology, 5*, 256-262.

McCabe, K., Houser, D., Ryan, L., Smith, V., & Trouard, T. (2001). A functional imaging study of cooperation in two-person reciprocal exchange. *PNAS, 98*(20), 11832-11835.

McCrae, R. R., & Paul T. Costa, J. (1987). Validation of the Five-Factor Model of Personality Across Instruments and Observers. *Journal of Personality and Social Psychology, 52*(1), 81-90.

Menon, M., Pomarol-Clotet, E., McKenna, P., & McCarthy, R. (2006). Probabilistic reasoning in schizophrenia: a comparison of the performance of deluded and nondeluded schizophrenic patients and exploration of possible cognitive underpinnings. *Cognit Neuropsychiatry, 11*(6), 521-536.

Mirowsky, J., & Ross, C. E. (1983). Paranoia and the structure of powerlessness. *American Sociological Review, 48*(228-239).

Mitchell, J. P., & Banaji, M. (2006). Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. *Neuron, 50*, 655-663.

Mitchell, J. P., Banaji, M. R., & Macrae, C. N. (2005). General and specific contributions of the medial prefrontal cortex to knowledge about mental states. *Neuroimage, 28*, 757–762.

Mitchell, J. P., Banaji, M. R., & Macrae, C. N. (2005). The link between social cognition and self-referential thought in the medial prefrontal cortex. *J. .Cogn. Neurosci, 17*, 1306-1315.

Mitchell, J. P., Heatherton, T. F., & Macrae, C. N. (2002). Distinct neural systems subserve person and object knowledge. *Proc. Natl Acad. Sci. , 99*, 15238–15243
Ndetei, D. M., & Vadher, A. (1984). Frequency and clinical significance of delusions across cultures. *Acta Psychiatr Scand 70*(1), 73-76.
North, A. S., Russell, A. J., & Gudjonsson, G. H. (2008). High functioning autism spectrum disorders: An investigation of psychological vulnerabilities during interrogative interview. *The Journal of Forensic Psychiatry & Psychology, 19*(3), 323-334.
Ochsner, K. N., Beer, J. S., Robertson, E. R., Cooper, J. C., Gabrieli, J. D. E., Kihsltrom, J. F., et al. (2005). The neural correlates of direct and reflected self-knowledge. *Neuroimage, 28*, 797 – 814.
Ochsner, K. N., Knierim, K., Ludlow, D. H., Hanelin, J., Ramachandran, T., Glover, G., et al. (2004). Reflecting upon Feelings: An fMRI Study of Neural Systems Supporting the Attribution of Emotion to Self and Other. *Journal of Cognitive Neuroscience, 16*(10), 1746-1772.
Overall, J., & Gorham, D. (1962). The brief psychiatric rating scale. *Psychological Reports, 10*, 799-812.
Owen, R. R., Fischer, E. P., Booth, B. M., & Cuffel, B. J. (1996). Medication noncompliance and substance abuse among patients with schizophrenia. *Psychiatric Services, 47*(8), 853-858.
Patrick, C. J., Curtin, J. J., & Tellegen, A. (2002). Development and validation of a brief form of the Multidimensional Personality Questionnaire. *Psychological Assessment, 14*(2), 150-163.
Paulus, M. P., Rogalsky, C., Simmons, A., Feinstein, J. S., & Stein, M. B. (2003). Increased activation of the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *NeuroImage, 19*, 1439-1448.
Pezze, M. A., & Feldon, J. (2004). Mesolimbic dopaminergic pathways in fear conditioning. *Progress in Neurobiology, 74*, 301–320.
Pinkham, A. E., Hopfinger, J. B., Pelfrey, K. A., Piven, J., & Penn, D. L. (2008). Neural basis for impaired social cognition in schizophrenia and autims spectrum disorders. *Schizophrenia Research, 99*, 164-175.
Pinkham, A. E., Hopfinger, J. B., Ruparel, K., & Penn, D. L. (2008). An Investigation of the Relationship Between Activation of a Social Cognitive Neural Network and Social Functioning. *Schizophrenia Bulletin, 34*(4), 688–697.
Poulton, R., Caspi, A., Moffitt, T. E., Cannon, M., Murray, R., & Harrington, H. (2000). Children's Self-Reported Psychotic Symptoms and Adult Schizophreniform Disorder: A 15-Year Longitudinal Study. *Arch Gen Psychiatry, 57*, 1053-1058.
Poundstone, W. (1992). *Prisoner's Dilemma* New York, NY: Doubleday.
Premack, D. W., W. (1978). Does the chimpanzee have a 'theory of mind'? *Behavioral and Brain Sciences, 4*, 515-526.
Raine, A. (1991). The SPQ: A scale for the assessment of schizoptypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin, 17*(4), 555-564.
Rotter, J. B. (1967). A new scale for the measurement of interpersonal trust. *Journal of Personality, 35*(4), 651-665.

Saarinen, P. I., Lehtonen, J., & Lonnqvist, J. (1999). Suicide risk in schizophrenia: an analysis of 17 consecutive cases. *Schizophrenia Bulletin, 25*(3), 533-542.
Sanfey, A. (2007). Social Decision-Making: Insights from Game Theory and Neuroscience. *Science, 318*(26), 598-602.
Sanfey, A. G., Rilling, J. K., Aronson, J. A., Nystrom, L. E., & Cohen, J. D. (2003). The neural basis of economic decision-making in the ultimatum game. *Science, 300*, 1755-1758.
Schmitz, T. W., Kawahara-Baccus, T. N., & Johnson, S. C. (2004). Metacognitive evaluation, self-relevance, and the right prefrontal cortex. *Neuroimage, 22*, 941-947.
Schneider, K. (1959). *Clinical Psychopathology*. New York: Grune and Stratton.
Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry., 59*(Suppl 20), 22-33.
Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*(3), 143-155.
Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23*(s1), 208-219.
Stompe, T., Friedman, A., Ortwein, G., Strobl, R., Chaudhry, H., Najam, N., et al. (1993). Comparisons of delusions among schizophrenics in Austria and Pakistan. *Psychopathology, 32*(5), 225-234.
Stompe, T., Ortwein-Swoboda, G., Ritter, K., Schanda, H., & Friedmann, A. (2002). Are we witnessing the disappearance of catatonic schizophrenia? *Comprehensive Psychiatry, 43*(167-174).
Tellegen, A., Ben-Porath, Y., McNulty, J. L., Arbisi, P. A., Graham, J. R., & Kaemmer, B. (2003). *The MMPI-2 Restructured Clinical (RC) Scales: Development, Validation, and Interpretation*. Minneapolis, MN: University of Minnesota Press.
Tellegen, A., & Waller, N. G. (2008). Exploring Personality Through Test Construction: Development of the Multidimensional Personality Questionnaire. In G. J. Boyle, G. Matthews & D. H. Saklofske (Eds.), *Handbook of personality theory and testing: Vol. II. Personality measurement and assessment* (pp. 261-292). London: Sage.
The-Psychological-Corporation. (2001). Wechsler Test of Adult Reading. San Antonio, TX: Harcourt Assessment.
Thesen, S., Heid, O., Mueller, E., & Schad, L. R. (2000). Prospective acquisition correction for head motion with image-based tracking foe real-time fMRI. *Magnetic Resonance in Medicine, 44*, 457-200.
Tomlin, D., Kayali, M. A., King-Casas, B., Cedric, A., Camerer, C. F., Quartz, S. R., et al. (2006). Agent-specifc responses in the cingulate cortex during economic exchanges. *Science, 312*, 1047-1050.
Walter, H., Adenzato, M., Ciaramidaro, A., Enrici, I., Pia, L., & Bara, B. G. (2004). Understanding Intentions in Social Interaction: The Role of the Anterior Paracingulate Cortex. *Journal of Cognitive Neuroscience, 16*(10), 1854-1863.

Williams, L. M., Das, P., Harris, A. W. F., Liddell, B. B., Brammer, M. J., Olivieri, G., et al. (2004a). Dysregulation of Arousal and Amygdala-Prefrontal Systems in Paranoid Schizophrenia. *Am J Psychiatry, 161*(13).

Williams, L. M., Das, P., Harris, A. W. F., Liddell, B. B., Brammer, M. J., Olivieri, G., et al. (2004b). Dysregulation of Arousal and Amygdala-Prefrontal Systems in Paranoid Schizophrenia. *American Journal Psychiatry, 161*, 480–489.

Williams, L. M., Dasa, P., Liddell, B. J., Olivieria, G., Peduto, A. S., Davide, A. S., et al. (2007). Fronto-limbic and autonomic disjunctions to negative emotion distinguish schizophrenia subtypes. *Psychiatry Research Neuroimaging, 155*, 29-44.

Wilson, J., & Enoch, M. (1967). Estimation of drug rejection by schizophrenic in-patients, with analysis ofclinical factors. *BritishJournal ofPsychiatry, 113*(209-211).

Winston, J. S., Strange, B. A., O'Doherty, J., & Dolan, R. J. (2002). Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nature Neuroscience, 5*(3), 277-283.

Zysset, S., Huber, O., Fersti, H., & von Cramon, D. Y. (2002). The anterior frontomedian cortex and evaluative judgment: An fMRI study *Neuroimage, 15*, 983-991.