ASSESSING FUNCTIONAL CONNECTIVITY AMONG A PUTATIVE RESPONSE INHIBITION NETWORK IN PEOPLE WITH SCHIZOPHRENIA

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ABSTRACT

ASSESSING FUNCTIONAL CONNECTIVITY AMONG A PUTATIVE RESPONSE INHIBITION NETWORK IN PEOPLE WITH SCHIZOPHRENIA

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Schizophrenia (SZ) is a psychotic disorder that results in, among other deficits, cognitive impairments that may affect a person's inability to integrate meaningfully into society, maintain interpersonal skills, and remain employed. Pervasiveness of cognitive impairments is recognized as a primary predictor of poor global outcome and chronic and is linked to long-term functioning. One of these impairments is response inhibition, the ability to withhold a prepotent response. Researchers have attempted to study this deficit by assessing response inhibition during performance of the stop signal task.

The dysconnection hypothesis of schizophrenia suggests that the symptoms of schizophrenia may result from impaired functional connectivity among neural structures. To examine this hypothesis, we used functional magnetic resonance imaging (fMRI) to assess functional connectivity among distinct neural structures involved in response inhibition. Subjects also were tested with a stop signal task. Our studies revealed the following: First, we observed large effect size deficits (ranging from 0.44 to 0.55) in functional connectivity at rest among structures involved in response inhibition and this

deficit was increased among the inpatient population. Second, we found evidence of continued functional dysconnectivity among regions during task performance among the inpatient population, a finding absent among the outpatient population. Additionally, behavioral results mimicked this pattern of deficit among the inpatient population. Third, as expected we observed a temporal stability of the resting state functional connectivity among controls. Interestingly, although outpatients initially exhibited decreased connectivity patterns at rest, these patterns normalized during the course of task performance as well as during the rest period following task performance. This pattern was not observed in the inpatient population.

Taken together, these findings suggest that people with schizophrenia exhibit impaired connectivity among structures in the response inhibition network at rest and during task and these deficits may be related to an impaired ability to control motor action, thus leading to undesirable behavior. In addition, the observed post-task normalization of the network among outpatients may suggest that they are able to better recruit these regions during task performance and may be reflective of improved symptomatology.

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INTRODUCTION

1.0 BACKGROUND

Schizophrenia (SZ) is a potentially debilitating psychiatric disorder that affects a person's perceptions, thought processes and behavior and generally manifests as hallucinations, delusions, paranoia and disorganized thoughts and behaviors (DSM-IV-TR, 2000).In the United States, SZ is thought to affect one percent of the population, approximately three million people. Although the prevalence rate of SZ is relatively equal among men and women, the peak age of onset is earlier in men than in women, between ages 20-28 in men vs. between ages 26-32 years in women (Robins and Regier, 1991; Riecher-Rossler, 2002).

Total direct and indirect health cost of SZ in the United States is estimated to be $63 billion dollars, with approximately $32 billion dollars due to lost employment potential (Wu et al., 2005; McEvoy, 2007). Additionally, approximately 46% of patients with SZ had at least one encounter with the legal system, with each encounter costing approximately $1500/patient (Ascher-Svanum et al., 2010).

SZ is recognized clinically by a varying range of signs and symptoms reflecting changes in cognition, emotion and perception (Lewis and Lieberman, 2000).Symptoms of SZ are divided into positive, negative and cognitive deficits. The term "positive symptom" refers to symptoms that are not normally present in healthy individuals but are present in people with SZ and includes delusions, hallucinations and thought disorders. "Negative symptoms" refer to abilities or behaviors that are normally present in healthy individuals but are absent in SZ individuals. Common negative symptoms include flat or blunted affect, alogia,

avolition and asociality and contribute more towards decreased quality of life and burden on others than positive symptoms (Velligan and Alphs, 2008). Cognitive deficits, which affect memory, attention and executive functioning can manifest as an inability to recognize and appropriately respond to social cues (Gopal et al., 2005) and may impact the patient's ability to maintain real-world functioning (Kraus et al., 2007). Pervasiveness of cognitive impairments is recognized as a primary predictor of poor global outcome and chronic disability (Harvey et al., 1990; Goldman, 1998; Green, 2006, Kay &Murrill, 1990), is linked to long-term functioning (Gopal et al., 2005) and is not consistently alleviated with traditional pharmacological interventions (McGurk, 1999; Smith et al., 2010).

Cognitive deficits, such as deficits in withholding a prepotent resonse (termed, response inhibition), have been shown in SZ (Lipszyc and Schachar, 2010; Nolan et al., 2010; Badcock et al., 2002). Both cortical and subcortical regions, such as the right inferior frontal gyrus, presupplementary motor area, the globus pallidus, the thalamus, the striatum and the subthalamic nucleus have been implicated in response inhibition tasks, such as the stop signal task (Duann et al., 2009; Eagle et al., 2004; Aron et al., 2006; Menon et al., 2001).

Functional connectivity between distinct neural structures can be assessed at rest and during task performance using functional MRI (explained in detail in section 1.4), and is known as resting state functional connectivity (RSFC) and task based functional connectivity (TBFC), respectively. Briefly, when functional connectivity is assessed at rest, subjects are instructed to lie still with their eyes closed or open and are thus scanned under non-task conditions.

Functional connectivity can also be assessed during task performance. Regions are said to be functionally connected if they are significantly correlated in their blood oxygen level dependent (BOLD) response. However, researchers have not assessed the functional connectivity between these regions within the response inhibition network in people with SZ. To address this gap in the literature, we propose to assess the functional connectivity among structures involved in response inhibition task in people with SZ and healthy controls we designed the following set of studies to: 1. Assess the functional connectivity, both at rest and during task performance, among neural structures involved in response inhibition and 2. To test the predictive utility of functional connectivity at rest and during task on behavioral performance, three main studies and two preliminary studies (contained in chapter 5) comprise the body of this thesis:

Study 1: RSFC among response inhibition structures in patients and controls. We assessed the RSFC among cortical and subcortical structures involved in response inhibition in patients and healthy controls and its relationship to behavioral performance on the SST.

Study 2a: TBFC among response inhibition structures in patients and controls. We assessed the TBFC among these structures in patients and healthy controls and its relationship to behavioral performance on the stop signal task.

Study 2b: Assess the psychophysiological interaction among regions involved in response inhibition during stop trials. In this chapter, we tested the functional connectivity among the structures involved in stopping a response during correct stop trials and error stop trials.

Study 3: Using functional connectivity to predict task performance on the stop signal task. In this study, we tested the predictive utility of using functional connectivity among response inhibition structures at rest and during task to predict behavioral performance on the stop signal task that recruits those structures.

Ancillary studies (Chapter 5):

Study 1: Assess between group differences among response inhibition using the STOP-IT task. In this, we tested subjects' performance on the STOP-IT task, a response inhibition task created by the author of the stop signal task.

Study 2: Modulation of resting state as a function of task. We assessed the modulatory effect of resting state functional connectivity pre and post task performance among patients and controls.

1.1 THE PLAN

This dissertation is organized as follows. In section 1.3, I first introduce and explain the widely established and accepted Dysconnection Hypothesis (DH) used to explain the symptoms of SZ and provide convergent evidence from various fields to lend support to the hypothesis. In section 1.4, I assess the utility of using functional connectivity as a tool for examining dysconnection in SZ. Finally, in section 1.5, I introduce and explain response inhibition and provide an in-depth description of the stop signal task (SST)that is used to test response inhibition. I conclude chapter 1 by addressing the limitations of previous studies and the contribution of this thesis in addressing these limitations.

Guided by the principles outlined in Chapter 1, in Chapters 2 and 3, I empirically assess the functional dysconnectivity of specific regions in SZ and its relationship to measures on the SST. In chapter 4, I provide results from two preliminary studies we conducted and in chapter 5, I conclude the dissertation with remarks on future directions in the study of dysconnectivity seen in SZ.

1.2 THE DYSCONNECTION HYPOTHESIS (DH) OF SZ

The idea that psychosis is not the result of focal brain abnormalities, but rather results from pathological interactions between *distinct* brain regions was first proposed by Wernicke in 1906 and later specifically applied to SZ by Bleuler in 1911, who first named the disorder to denote a "splitting of the mind" (Stephan et al., 2006). Bleuler suggested that SZ arises from anatomical disruption of association fiber tracts which results in the "splitting" of different mental domains, an idea that gained further support by the advent of techniques such as fMRI and ERP (Volkow et al., 1988; Hoffman et al., 1991; Weinberger et al., 1992; Friston and Frith,1995).

In 1991, Javitt & Zukin suggested that the symptoms of SZ are more aptly explained as a function of NMDA-R functioning (in contrast to the dopamine hypothesis of SZ which predominantly explains only the positive symptoms of SZ),because such impairment mimics the positive, negative and cognitive symptoms observed in SZ.

In an effort to provide a unifying neurobiological explanation for these observed empirical data, Karl Friston (1995) proposed the disconnection

hypothesis (later amended to the *dysconnection* hypothesis. See Stephan et al., 2009 for a review)[1]. Although there is no consensus regarding the exact pathophysiology of SZ, Friston's dysconnection hypothesis (DH; 2006)(Stephan et al., 2009) has gained wide acceptance as a leading theory used to explain the symptoms (and not the *cause)* of SZ. The dysconnection hypothesis suggests that the core pathology of SZ is impaired neuromodulation of synaptic plasticity of N-methyl D-aspartate receptors (NMDA-R) by neuromodulatory transmitters such as dopamine (DA), acetylcholine (Ach) or serotonin (5-HA) (determined by factors such as experience dependent plasticity) which leads to abnormal functional integration of neural systems and thus reflects aberrant modulation and facilitation of changes in connection strength. Additionally, the impaired functioning of the NMDA-R, in turn, impairs the functioning of the GABAergic neurotransmitters (Stephan et al., 2009). As such, the specific signs observed in SZ (positive, negative and cognitive) may be result of impaired modulation of synaptic plasticity (specifically, impaired reinforcement of synaptic plasticity) by these neuromodulatory transmitters.

Convergent evidence from various fields lends support to the idea that SZ is a functional dysconnection syndrome. Neuroimaging studies suggest widespread disintegration among cortical and subcortical structures in people

[1]The disconnection hypothesis (and thus disconnectivity among structures) of SZ, introduced by Friston in 1995, suggests that SZ can be understood in terms of decreased integration among neural structures. Because this term suggests that the connectivity among neural structures is necessarily reduced, Stephan et al., (2006) introduced the term "dysconnectivity" to explain findings that reflect both reduced and increased functional interactions. Thus the term "dysconnectivity" is used to emphasize the notion of *abnormal* and not necessarily decreased functional integration among distinct brain regions.

with SZ (Liu et al. 2006; Liang et al. 2006). Decreased RSFC between the dorsolateral prefrontal cortex (DLPFC), the posterior cingulate cortex (PCC) and the thalamus (Thal) is well established in both chronically ill patients (Callicott et al. 2000) and those with first episode SZ (Zhou et al. 2007). A recent study by Tu et. al. (2010) showed that reduced functional connectivity of the right cingulate eye field with the posterior parietal cortex disrupts connectivity in the network for spatial attention and volitional ocular motor control.

Studies have consistently shown that the generation of mismatch negativity (MMN), which may be dependent on synaptic plasticity, is significantly reduced in patients (Javitt et al., 1996; Salisbury et al., 2002; Bramon et al., 2004; Baldeweg et. al., 2006; Rasser et al., 2009). MMN, typically elicited during prediction errors in implicit learning tasks (Stephan et al., 2006; Friston, 2005),can be blocked by the administration of NMDA antagonists such as ketamine (Umbricht et al., 2000). In humans, this plasticity is modulated by acetylcholine (Ach) and 5-HT, both of which alter the MMN (Baldeweg et. al., 2006). Additionally, studies suggest that delusions in SZ may be due to abnormal reinforcement learning, which is dependent on DA modulation of NMDA receptor mediated synaptic plasticity. Similarly, cognitive deficits in SZ may be due to abnormal Ach modulation of NMDA receptor mediated synaptic plasticity (Baldwin et al., 2002; Smith-Roe et al., 2000).

Postmortem studies have demonstrated a number of consistent changes in the brains of people with SZ that may be due to impaired synaptic plasticity.

Specifically, the observed reduction in dendritic field size and dendritic spines of cortical neurons (Black et al., 2004; Garey et al., 1998) may be due to impairments in the NMDA-receptors (NMDAR) responsible for promoting dendritic growth and spine formation (Monfils et al., 2004). Changes in glutamate receptor binding and subunit protein expression have been observed in the prefrontal cortex, Thal and hippocampus of subjects with SZ (Clinton & Meador-Woodruff, 2004), providing further support for the dysconnection hypothesis of SZ.

Genetic studies show that SZ is a strong familial disorder as evidenced by the majority of the candidate genes for SZ that play a role in NMDA-R dependent signaling and plasticity (Harrison & Weinberger, 2005) by influencing the function of modulatory sites on the NMDAR (Harrison et al., 2003, Egan et al., 2004; Javitt 2007).

1.3 Neural Connectivity

"Neural connectivity" refers to a pattern of anatomical links(structural connectivity), of statistical dependencies (functional connectivity) or of causal interactions (effective connectivity)between distinct units within a nervous system that may constitute individual neurons, neuronal populations, or anatomically segregated brain regions.

Structural and Effective Connectivity

"Anatomical connectivity" (AC) refers to structural connectivity between two regions via the white matter axonal projections connecting spatially distinct

regions and can be studied using diffusion tensor imaging (DTI), a magnetic resonance imaging technique that examine the directionality and magnitude of water diffusion in *in vivo* axonal fibers. Thus, DTI can be used to study the integrity of the white matter tracts and the technique has been used to study white matter deficits in SZ (Lim et al., 1999). Effective connectivity (EC) describes the influence of one region over another (either at the level of the synapse or at the cortical level among distinct regions) and gives information about the causal relationship between them (Friston et al., 1994). This analytic method is used when it is not simply enough to know that areas are similarly modulated during a given task (Wang et al., 2010).

Functional Connectivity

Regions of the brain are correlated in their blood oxygen level dependent (BOLD) response and this correlated vascular response is thought to underlie coherent neural signal (Biswal et al., 1995). This underlying correlated neural activity, thought to serve a function—from cognitive monitoring to concerted recruitment of areas during task, falls under the umbrella term “functional connectivity.” Functional connectivity (FC) is the statistical association (or temporal correlation) of the BOLD response between remote neurophysiological events. This connectivity may or may not reflect *direct* anatomical connectivity (see Figure 1).

FC can be assessed under two conditions: during a task(termed task based functional connectivity, TBFC) or non-task condition (termed resting state

functional connectivity, RSFC). Since the BOLD signal in RSFC is assessed during non-task conditions, it is also termed spontaneous signal.

*Resting State Functional Connectivity (RSFC)*Spontaneous neural activity is not attributable to specific inputs or outputs; it represents neuronal activity that is intrinsically generated by the brain at rest. “At rest” is defined as periods during which the subject is not engaged in task-related activity. S/he is told to lie still.

RSFC displays properties such as spatial coherence and functional topography that rules out the possibility of it just being random noise (Fox& Raichle, 2007).*Spatial coherence:* The initial observation of coherent BOLD activity in the somatomotor cortices (Biswal et al., 1995) has been replicated in many other sets of brain regions, such as the default mode network (Raichle, 2001), the visual and auditory network (Cordes et al., 2001) and the dorsal and ventral attention systems (Laufs et al., 2003). These observations led to the conclusion that areas that are similarly modulated under task paradigms tend to be correlated in their spontaneous BOLD activity (Fox & Raichle, 2007). *Temporal coherence:* The temporal properties of spontaneous fluctuations lends further support to the idea that the observed fluctuations do not reflect random noise. Spontaneous fluctuations follow a 1/f distribution, such that lower frequencies are present at increasing power (Fox & Raichle, 2007). Cordes et al., (2001) showed that frequencies at 0.1 Hz contribute to the spatially coherent spontaneous BOLD signal. In partial support of the DH, impairment in widespread RSFC has been shown in people with SZ (Liu et al. 2006; Liang et al.

2006). Liang et al. (2006), who conducted the first resting state analysis in people with SZ, employed a voxelwise approach to examine the functional connectivity of the whole brain of people with SZ. They divided the brain into 116 regions and performed paired correlational analysis to determine the strength of temporal synchrony. Widespread disintegration between cortical and subcortical structures was observed. Similar widespread decreases in functional connectivity have been observed in other studies (Liu et. al., 2006; Bluhm et al., 2007; Wolf et al., 2007).Additionally, Garrity et al., (2007) showed significantly increased functional connectivity among the following region pairs: left and right anterior cingulate, parahippocampal gyrus, and posterior cingulate and in the superior and medial frontal gyri and the left middle frontal and temporal gyri.

Targeted, regionally specific areas in the brain of people with SZ also show decreased functional connectivity. RSFC between the DLPFC, a structure extensively implicated in cognitive functioning, and the PCC and the Thal is significantly decreased in first-episode patients (Zhou et al. 2007; Callicott et al. 2000). Hoptman et al. (2009) extended our understanding of resting state and its relationship to psychopathology by assessing the relationship between the amygdalofrontal connectivity and its relationship to aggression. They showed that decreased amygdalofrontal connectivity is negatively associated with self-reported aggression. These studies suggest the cognitive and behavioral relevance of RSFC.

Although impaired performance on the SST has been observed in people with SZ (Badcock et al., 2002; Nolan et al., 2011) and the relevant neural structures that contribute to the SST have been identified (Aronet al., 2006; Li et al., 2008; Aron et al., 2003), RSFC among these neural structures has not been explored. Our work attempts to address this gap in the literature.

The behavioral significance of BOLD RSFC is not well understood. However, it may be directly related to the variability in behavioral performance (Fox, et al. 2007).Task-based activations, as assessed by fMRI, can be viewed as a combination of changes attributed to the presentation of, and response to, a task and to ongoing resting state spontaneous fluctuations (Fox and Raichle, 2007). Fox and Raichle (2007) demonstrated a relationship between spontaneous brain activity in the left somatomotor cortex and trial-to-trial variability in button press force. He et al. (2007) suggested that the degree of RSFC disruption within the ventral and dorsal frontoparietal attention networks correlated with the severity of spatial neglect. Connectivity in these two largely separate attention networks was assessed at both acute and chronic stages of recovery. Disrupted connectivity in specific pathways in the ventral attention network strongly correlated with impaired attentional processing across subjects. Similarly, reduction of RSFC in the dorsal attention network was behaviorally significant. There was a strong correlation between the strength of the interhemispheric RSFC in the dorsal parietal cortex and detection of targets in the left visual field following an invalid cue, such that the lower the interhemispheric RSFC in the dorsal attention network (in particular, the dorsal

parietal cortex), the more impaired patients were in reorienting attention toward the neglected visual field. Critically, this correlation remained highly significant even after correcting for lesion size and movement. Similar findings of correlation between RSFC and behavior were reported in Margulies et al., 2007; Castellanos et al. 2008 and Di Martino et al. 2008.

Importantly, patterns of spontaneous activity may provide *a priori* hypotheses about the way in which the brain will respond across a wide variety of task conditions. This suggests that we can, by looking at the resting state data, predict how the regions will respond under task conditions.

To our knowledge, the relationship between RSFC and its correlation with behavioral performance on the SST in people with SZ has not been established. We hypothesize that the abnormal RSFC seen in people with SZ will be correlated with decreased performance on the SST.

Task Based Functional Connectivity (TBFC)

The low frequency fluctuations observed at rest continue during task (Fox& Raichle, 2007) any may play a role in task performance. “TBFC” refers to functional connectivity observed under task conditions between structures that are activated or deactivated in the service of some goal. Because there is no uniform terminology used to describe connectivity assessed during task conditions, we introduce the term task based functional connectivity (TBFC). A limited number of studies have attempted to assess the effects of TBFC on behavioral performance in people with SZ (Wolf et al., 2009; Boksman et al.,

2005; Honey et al., 2005; Meyer-Lindenberg et al. 2001). Boksman et al., (2005) studied the functional connectivity patterns between the prefrontal cortex (PFC), the Thal and the left ACC in first episode patients with SZ during a working memory task. Results implicate reduced temporal correlation among these regions during task with deficits in task performance. Similarly, impaired TBFC was observed between the DLPFC and the PCC in chronically ill patients during performance on an N-back working memory task (Callicott et al., 2000). Wolf et al., (2009) showed that during a working memory task, patients with SZ exhibited abnormal TBFC, namely, significantly increased connectivity (as compared to healthy controls) in the bilateral DLPFC and the left anterior parietal cortex, regions commonly activated with working memory processing.

However, to our knowledge, no studies have assessed the TBFC of regions recruited in the performance of the SST. We will attempt to address this gap in the literature.

Psychophysiological Interaction Analysis

TBFC can also be assessed as a function of task conditions, in an fMRI functional connectivity analysis known as psychophysiological interaction (PPI). PPI gives information about task specific changes in functional connectivity among areas (Friston et al., 1998; Gitelman et al., 2003).

The basic PPI model can be expressed as:

Equation 1: $$H(s)=H(t)+H(s*t),$$

Where H=hemodynamic response function,
t=task, and
s*t=interaction between seed region and task

Simply put, when the activity of a particular neural region is regressed on the activity of a second neural region, the slope of this regression reflects the influence one region exerts over the other. Assessing the change in the slope of the regression line under a different behavioral context and comparing this change across the two contexts is known as PPI (Friston et al., 1997).

Recent studies show altered PPI among people with SZ compared to healthy controls (Wang et al., 2011, Harvey et al., 2011). Wang et al., (2011) showed that healthy controls exhibited increased connectivity between the medial prefrontal cortex (mPFC) and the left superior temporal gyrus (LSTG) in the Other vs. Self condition of a source monitoring task. This effect was reversed for the patient population who showed greater mPFC-LSTG connectivity during the Self vs. Other condition suggesting that they recruit regions that are normally involved in retrieving “other generated” information during self-generated information. Similarly, Harvey et al., (2011) showed that the increased coupling between the lateral occipital complex(LOC) and fronto-parietal regions during visual backward masking task in healthy controls reflects visual reentrant processing. The absence of such a coupling between LOC and fronto-parietal regions in SZ may contribute to abnormalities in visual perception (Doniger et al., 2000; Sehatpour et al., 2008).

Although studies assessing PPI in SZ are becoming more common, there are currently no studies that assess the PPI among response inhibition structures under various task conditions. To address this gap in the literature, we assessed the PPI among the rIFG and the rest of the brain under the stop correct and stop incorrect conditions of the stop signal task (explained in more detail in section 1.5).

1.4 FC AS A TOOL FOR EXAMINING DYSCONNECTION IN SZ

Regions of the brain are correlated in their BOLD response and this correlated response is thought to underlie coherent neural signal (Raichle et al., 2006).The use of functional magnetic resonance imaging (fMRI) to assess connectivity patterns is particularly relevant in this context, because functional connectivity (and its subcomponents, RSFC and TBFC), at its core, provides information about interregional coordinated neural activity. As mentioned above, the dysconnection hypothesis of SZ states that the observed deficits of SZ can be explained by the abnormal interactions between neural structures. Thus, the use of functional connectivity to assess the level of coordinated activity among regions is applicable.

1.5 RESPONSE INHIBITION

"Impulsivity" refers to acting without thinking and can lead to unfavorable outcomes, including high-risk sexual behavior, substance abuse and aggression. Impulsivity is a heterogeneous concept, consisting of both response inhibition and poor decision making (Christodoulou et al., 2006) and research suggests

that impulsivity, response inhibition and poor decision making may result from a similar neurobiological impairment. Hoptman et al., (2004) showed that impulsivity in people with SZ is related to inferior frontal regions, in particular, a negative correlation between white matter integrity within the right ventro-medial prefrontal region and motor impulsivity. This suggests a possible structural cause of the observed increase in impulsive behavior.

The ability to change or stop an ongoing action in order to fulfill an updated goal is a hallmark of executive functioning and is referred to as response inhibition. The ability to stop has been extensively studied and the stop latency data from young adults across varying modalities show that, on average, adults stop a response in about 200 milliseconds (Logan et al.,1984), lending support to the idea of a unitary mechanism underlying response inhibition.

Response inhibition can be further categorized into reactive and proactive inhibition and the two types can be distinguished from each other by how they are initiated. Reactive inhibition is always initiated by an external cue, such as a stop signal, and is transient following this event. In contrast, proactive inhibition is guided by internal processes, prevents a response to a subsequent event and can be sustained across multiple trials. Because the stop process in the stop signal task begins only after an external stop cue is presented, the SST is considered to study reactive inhibition (Wardak, 2011; Zandbelt et al., 2011).

The SST can be used to examine response inhibition deficits in psychopathological populations. For example, Logan et al.(1989) found that

children with hyperactive disorder performed significantly worse than their non-hyperactive counterparts. People with SZ also exhibit abnormal response inhibition (Badcock et al. 2002; Bellgrove et al. 2006; Weisbrod et al. 2000; Perlstein et al. 2003; Barch et al. 2001).

Neurocognitive studies in people with SZ show a wide range of impairments across modalities including memory, attention, inhibition and volitional motor control (Tu et al., 2010; Wolf et al., 2009; Bellegrove et al., 2006; Bilder et al., 2000). Additionally, studies of response inhibition in people with SZ suggest impairments of prefrontal/executive abilities (Mahurin et al. 1998; Hill et al., 2004; Twamley et al. 2006; Huddy et al., 2009; Thoma et al., 2007; Kaladjian et al., 2007; Bellgrove et al., 2006), possible upstream of sensory deficits (Javitt et al., 2009).

Response inhibition can be empirically studied using the stop signal task (SST). The assumptions and predictions made from the SST are based on the independent race model (Logan et al., 1984; see Figure 2).

According to this model, performance on the SST is modeled as a race between two independent processes, the go process, which begins at the presentation of the go stimulus and the stop process, which begins at the presentation of the stop stimulus. If the stop process finishes before the go process reaches the point of no return, then the subject correctly withholds a response. The *point of no return* represents the threshold between a ballistic process and one that can be controlled (De Jong et al., 1990; Osman et al.,

1986, 1990). However, if the stop process finishes after the go process reaches the point of no return, then the response is emitted. The Go process of the SST is easily observed whereas the Stop process must be calculated indirectly. The independent race model provides a theoretical framework for inferring the stop latency, the stop signal reaction time (SSRT). The SSRT value provides the basis of most of the conclusions drawn about inhibition behaviors (Logan et al., 1984). Specifically, longer SSRT indicates poor response inhibition, and many studies have used prolonged SSRT as an index of impaired motor inhibitory control in patients with neurological or psychiatric conditions (Kooijmans et al., 2000; Rieger et al., 2003; Gauggel et al., 2004; Bekker et al., 2005; Bellgrove et al., 2006; Alderson et al., 2007; Sagaspe et al., 2007; Huddy et al., 2009; Huizenga et al., 2009; McAlonan et al., 2009). It can be calculated using multiple methods, each with different underlying assumptions. The various methods capitalize on the relationship between the horse race model (see Figure 2) and the inhibition function in order to calculate the SSRT. The inhibition function is a graphical representation of the p(inhibit|signal) as a function of the stop signal delay (see Figure 3).

SSRT is commonly calculated as the difference between the mean go signal reaction time and the mean of the inhibition function. Formally, it is expressed as:

Equation 2: $\overline{T}_s = \overline{T}_g - \overline{T}_i$

T_s=Mean SSRT

T_g=Mean of Go reaction time
T_i=Mean of the inhibition function

T_g is easily calculated from the observed reaction times to correct go signal. Calculating T_i is considerably more complicated and can be computed in several methods: Method 1. The mean of the inhibition function is $\Sigma p_i x_{i,}$ where p_i is the probability of responding at the *i*th SSD minus the probability of responding at the *i*-1th SSD and x_i is the *i*th SSD. Method 2. Alternatively, if one makes the assumption that the inhibition function has a symmetrical distribution, then one can use the median of the inhibition function to calculate the SSRT because the mean and the median will be identical (in a normally distributed sample). The median is simply the point at which p(inhibit)=p(respond), which is 50%. Based on the ease of computation of Method 2 along with studies (Logan et al., 1984; Logan, 1994) showing reasonable agreement between the mean of the inhibition function using Method 1 and median of the inhibition function using Method 2, the latter method is the recommended method (Logan, 1994). In our studies, we used Equation 2 to calculate SSRT and method 2 to calculate the mean of the inhibition function.

Importantly and often overlooked part of the independent horse race model it depends on the relative *finishing* time of the go and the stop process and not on the relative *starting* time. The probability of responding to a stop signal will be the same for different conditions even though the SSD, SSRT and the underlying distribution of the go distribution may be different, provided that the relative finishing time of the go and the stop process is the same. This allows for

inhibition functions from different subject population, tasks or conditions to be aligned by plotting the probability of responding to a stop signal p(respond|signal) against the relative finishing time but may be misaligned when it is plotted against the relative starting time of the go and the stop process. The alignment process, proposed by Logan et al., (1984) takes into account the variability of the go reaction time among the different populations. Because variability in go reaction time influences the inhibition function (i.e. the inhibition function is shifted to the right, see Figure 4) even when the mean go reaction time remains constant.

The method takes differences in mean go reaction time and the stop signal reaction time into account and plots inhibition functions in terms of a Z score and thus plots the p (respond|signal) against the relative finishing time (RFT), the go and stop process in standard deviation units, resulting in a Z-score:

Equation 3: $$\text{ZRFT: } (RT_{go} - SSD - SSRT)/SD_{go}$$

$ZRFT_{=}$ Z-score transformation of the relative finishing time
RT_{go}= Mean go reaction time
SSD= Stop signal delay
SSRT=Stop signal reaction time
SD=Standard deviation of the go distribution

Stop Signal Task

In our version of the stop task, participants are presented with either a letter “X” or a letter “O.” They are told to press the right button when the letter “X” is presented and the left button when the letter “O” is presented. These represent the Go stimuli since the subjects are not told to inhibit their responses. In the

Stop stimuli condition (25% of trials), the letter “X” or “O” is followed by a red square.

The time between the presentation of the “X” stimulus and the “O” stimulus, the SSD, was dynamically changed from 250 ms to 750 ms in accordance with the subject’s performance, such that when the subject correctly withheld a response during the stop trial, the SSD increased by 50 ms, up to a maximum SSD value of 750ms. Alternatively, if the subject responded incorrectly to a stop trial, then the SSD decreased by 50 ms, down to a minimum SSD value of 250ms. These adjustments were made on the assumption that dynamically varying the SSD would yield a p(inhibit) of 50% and that as SSD increases, the subject is more likely to respond during a stop condition and vice versa. This assumption is the key to understanding the inhibition function and how SSRT can be calculated. In addition to the SSRT, other measures such as stop and go accuracy can also be determine.

Go accuracy is calculated as:

Equation 4:

$$\frac{\#\text{ Correct Go Trials}}{\text{Total \# of Go Trials}}$$

I argue for and utilize an alternate method of calculation. In this method, correct stop trials (the value in the numerator) is defined as those correct stop trials that are preceded by a go trial in which the subject responded. In this way, we can eliminate stop trials during which the subject is not involved in response inhibition but is rather is idly sitting. Therefore, in these cases, although the subject responds correctly to a stop trial (because she didn’t press a button), I argue that inclusion of these trials biases the results towards increase inhibition.

However, by only including those stop trials that are immediately preceded by a go trial in which the subject responded, we can decrease the likelihood of irrelevant trials and thus ensure that we are actually testing that which we seek to test.

Equation 5:

$$\frac{\text{\# Correct Stop Trials}}{\text{Total \# of Stop Trials}}$$

The STOP-IT task

A subset of subjects, as described in Chapter 4, participated in 4 blocks of the STOP-IT task (Verbruggen et al., 2008). Subjects are presented with a primary task, differentiating circle and square. On no-signal trials, which account for 75% of trials, subjects are instructed to respond to the stimulus as fast and accurately as possible. On stop-signal trials, which account for 25% of trials, the primary task is followed by an auditory stop signal (750Hz, presented for 75 ms, and subjects are instructed to withhold their response. The data are collected and saved as a tab-delimited text file.

Neural correlates of response inhibition:

Studies using the SST have identified the right inferior frontal gyrus (rIFG), the presupplementary motor area (preSMA), the subthalamic nucleus (STN), the globus pallidus (GP), the striatum (ST), and the Thalamus (Thal) as being consistently recruited during task performance (Aron et al., 2006). Thus, these structures can be conceptualized as forming a putative response inhibition network. Studies using anatomical and effective connectivity have shed light into the neural pathway of response inhibition. A theory known as the basal ganglia

model of response inhibition suggests that response inhibition pathways project through the basal ganglia; specifically, projections from frontal cortex (such as the rIFG) to the GP, via the ST and the STN, and then back to the cortex via the Thal. (Mink,1996; Nambu et al., 2002; Aron, 2010).However, the relative contribution of these specific pathways to inhibitory control remains elusive (See Figure 5). Note however, that the initial Aron model of response inhibition does not include the effects of the preSMA. To include its contributions to the response inhibition pathway (Duann et al., 2009, Jahfari et al., 2011), a modified network is shown (See Figure 6).

Right Inferior Frontal Gyrus: In fMRI studies of response inhibition, the rIFG has been shown to be consistently activated (Konishi et al., 1999; Menon et al., 2001;Rubia et al., 2003; Aron et al., 2003; Chambers et al., 2006; Verbruggen, 2008), whereas other regions of the prefrontal cortex are not. Further, animal studies show that the greater the damage to this region, the worse the monkeys performed on response inhibition, as measured by the SSRT (Iversen et al., 1970).Following lesion studies that showed increased deficits in response inhibition as a function of damage to the rIFG, Garavan et al., (1999) and Aron et al., (2003) concluded that the rIFG is unilaterally involved in response inhibition. This notion remained unchallenged until a series of elegant studies by Hampshire et al. (2010) and Duann et al. (2009) showed that the rIFG is activated during non-inhibition conditions. Thus, the evidence suggests that the rIFG may not directly mediate motor response inhibition per se but rather aids in detection of salient target (such as detection of the stop signal). Once the salient

target is detected, the rIFG influences the basal ganglia circuitry indirectly via the presupplementary motor area to inhibit action.

Presupplementary Motor Area: Using functional connectivity analysis, Duann et al., (2009) delineated the functions of the rIFG and the preSMA. Specifically, they demonstrated that the preSMA has direct connectivity to the basal ganglia whereas the rIFG does not. The implication of this connection is that the preSMA and not the rIFG is in a unique position to engage the go and the stop process once the rIFG detects the salient cue. Psychophysiological (PPI) interaction analyses showed greater functional connectivity among the rIFG and the preSMA during correct stop trials as compared to error stop trials (Duann et al., 2009).

Subthalamic nucleus: The STN is a subcortical structure that is functionally part of the basal ganglia and is located ventrally to the Thal and receives its primary input from parts of the pallidum and the frontal cortex (Aron et al., 2006). The primary neurons within the STN are the excitatory, glutamatergic neurons—which is in contrast to the other structures in the basal ganglia that project inhibitory, GABAergic projections. The presence of excitatory projections within the subcortical structures makes the STN in a unique position to change the outcome of the network. Although the STN receives most of its projections from the GP, it also receives excitatory, glutamatergic projections from the cortex as well as dopaminergic projections from the substantia nigra pars reticulate (SNr), another component of the basal ganglia network. Recent work in patients with Parkinson's disease implicates the STN in stop signal inhibition (Frank et al., 2007) and STN lesions in the rat brain is associated with slower SSRT (Eagle et

al., 2004). Although the exact role of the STN in motor inhibition is not fully understood, study by Aron and Poldrack (2006) suggests that the STN may be differentially activated as a result of whether the go process has already begun on not. For example: During trials of short SSD, the go process hasn't come "online" for long, the response inhibition network does not function via the STN and may use the hyperdirect pathway of the basal ganglia. This hyperdirect pathway bypasses the STN and sends inhibitory control to the motor cortices, resulting in the remission of motor movement. If however, the SSD is longer, and thus the go response is near execution, inhibition may operate at a later stage and include the STN to prevent movement. This longer pathway is known as the indirect pathway of the basal ganglia.

Globus Pallidus: The GP is a subcortical structure that is a subcomponent of the basal ganglia and receives strong glutamatergic projections from the STN (Aron et al., 2006).The basal ganglia is associated with motor control and is involved in controlling subconscious voluntary movement. The globus pallidus transmits information from the putamen and caudate to the thalamus.

Striatum: Stopping a motor response requires suppression of the primary motor cortex and has been linked to activation of the striatum (Zandbelt & Vink, 2010). The ST receives efferent projections primary from the cortex, although it also receives minor projections from the STN and the GP. Primary afferent projections are to the GP (Aron et al., 2006).

Thalamus: The Thal is a subcortical structure located in the midline on either side of the third ventricle. The Thal has been shown to be active in response inhibition

paradigms (Menon et al., 2001; Aron et al., 2006; Liddle et al, 2001), particularly in stop conditions.

The go process activation of the basal ganglia pathway

The go process of the SST, which represents the primary task condition begins with the presentation of the “X” or “O.” Many studies show that the go condition predominantly activates bilateral striatum, left thalamus, left preSMA, left motor cortex, and the left GP, consistent with right-hand response (Aron & Poldrack, 2006; Liddle et al., 2001). As such, the go condition of the task activates motor responses via the fronto-striato-pallidal pathway of the basal ganglia.

The stop process activation of the basal ganglia pathway

The stop process of the SST, which represents the infrequently presented secondary task condition, begins with the presentation of the red square. At a small SSD, the go network has not been “online” for long and the response inhibition operates on a different stage of the motor planning system, i.e. the hyperdirect pathway. This pathway occurs in instances of fast stop responses. If, however, the SSD is larger, then the go network has had the opportunity to come “online” and thus is close to completing the go action. In this instance, the inhibition network operates using a different aspect of the network, i.e. the indirect pathway. This pathway inhibits action via activation of the STN by the cortico-striatal pathways and results in a net inhibition of the thalamocortical

fibers. Studies by Aron & Poldrack, 2006, show that the stop process activates the thalamus, STN and GP bilaterally as well as the rIFG, right pre-SMA, suggesting a right-side laterality effect of inhibition.

Deficits in SST performance in people with SZ have been demonstrated. Specifically, people with SZ exhibited increased SSRT as well as greater response variability (Nolan et al., 2011; Lipszyc & Schachar, 2010). However, the nature of underlying neural connections among structures within the response inhibition network has not been established in this disorder.

1.6 Contribution of This Thesis

Current literature shows the following: 1. Widespread resting state functional dysconnectivity has been observed in people with SZ. However, the dysconnection among the regions involved in SST has not been established. 2. Deficits in TBFC are ill established in people with SZ and, to our knowledge, unstudied in the SST response inhibition literature. 3. Studies demonstrate that the resting state fluctuations continue during task performance and may be related to task activations. However, the relationship between RSFC and TBFC and behavior has not been thoroughly investigated in people with SZ.

As such, we present a set of studies that will help address these gaps in the literature. The goals of the present study are to evaluate the degree to which deficits in functional connectivity (resting and task-based) is associated with impairment in performance on the SST. This will allow us to better understand

the underlying neural mechanisms involved in successful stop behavioral responses in the SST. To that effect, the following hypotheses were tested:

Study#1: To examine RSFC among regions that subserve the SST in people with SZ and healthy controls and to assess the relationship between RSFC and behavioral performance on the SST.

Hypothesis a: To date, the integrity of the RSFC between RI-relevant regions in people with SZ has not been established. We hypothesize that, at rest, people with SZ will show decreased temporal correlation of BOLD contrast response within the ROI region pairs as compared to healthy controls.

Hypothesis b*:* We hypothesize a negative correlation between RSFC and task performance such that decreased RSFC between the ROIs will be correlated with poorer task performance on the SST.

Study#2: To examine the TBFC between the ROIs in people with SZ and healthy controls and to assess its relationship to behavioral performance.

Hypothesis a: We hypothesize that people with SZ will show decreased TBFC among areas that are modulated activated during the SST as compared to healthy controls.

Hypothesis b: We hypothesize a positive correlation between TBFC and behavioral performances on the SST.

To examine the predictive utility of TBFC and RSFC in predicting behavioral performance.

Hypothesis a:We hypothesize that both RSFC and TBFC will be predictive of behavioral performance in controls and patients.

Assess the psychophysiological interaction among regions involved in response inhibition during stop trials.

Hypothesis a: We hypothesized that correct stop trials would be associated with greater connectivity among the preSMA and the rIFG when compared to error stop trials.

Hypothesis b: Although we expect to see this in both controls and patients, we hypothesize that there will be a between group difference in the extent of connectivity during correct stop trials.

Ancillary Studies:

Study #1: Assess the between group difference on behavioral performance on the STOP-IT task.

Hypothesis a: Based on the STOP-IT task's adherence to the principles explained in Logan (1994), we hypothesize that people with SZ would show increased SSRT when compared to healthy controls.

Study #2: Assess RSFC as a function of task among patients and controls.

Hypothesis a: We hypothesis that controls, but not patients will show an increase in RSFC post task.

Figure 1: RSFC between two ROIs in a healthy control

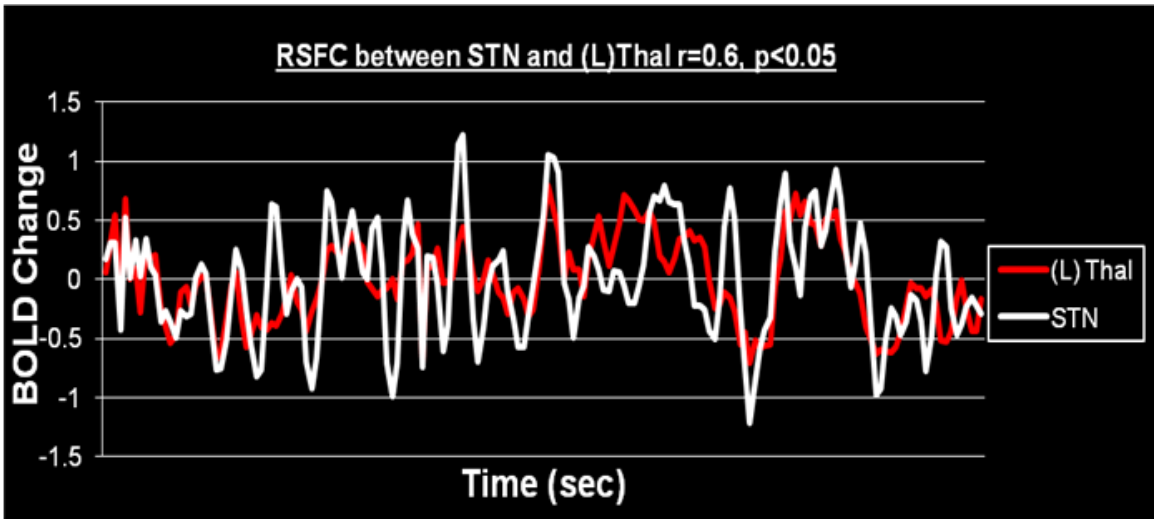


Figure 2: The Independent Horse Race Model (Figure from Verbruggen & Logan, 2009)

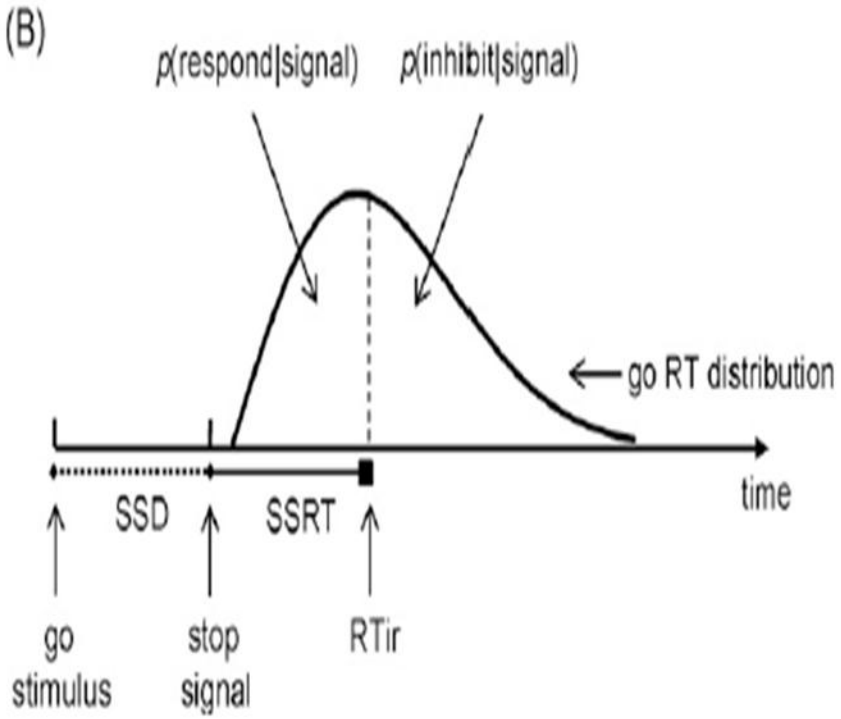


Figure 3: The horse-race model and its corresponding response inhibition function (Figure from Verbruggen and Logan, 2009)

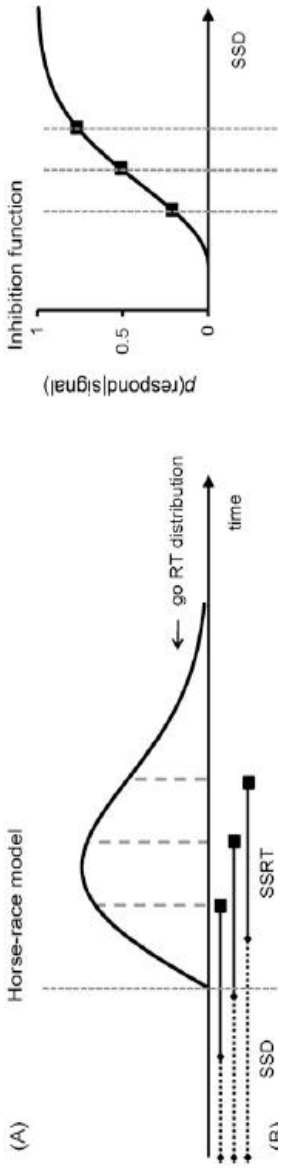


Figure 4: Change in the response inhibition function as result of altered go reaction time (Figure from Verbruggen & Logan, 2009).

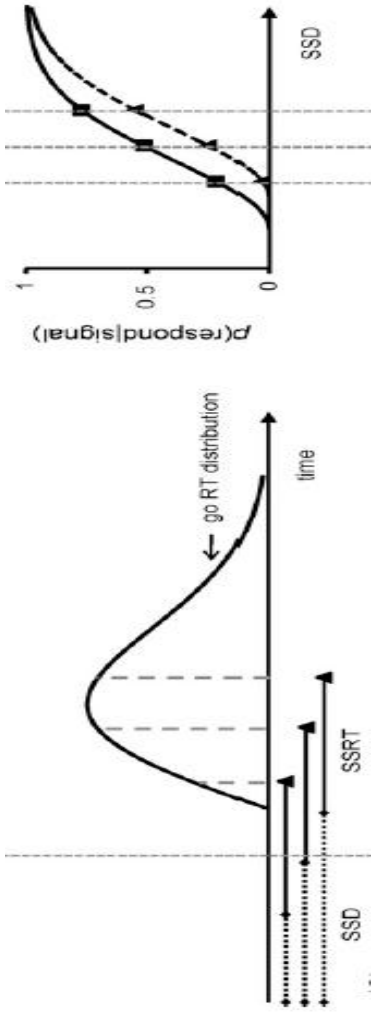


Figure 5: The basal ganglia model of response inhibition (Figure from Aron et al., 2006)

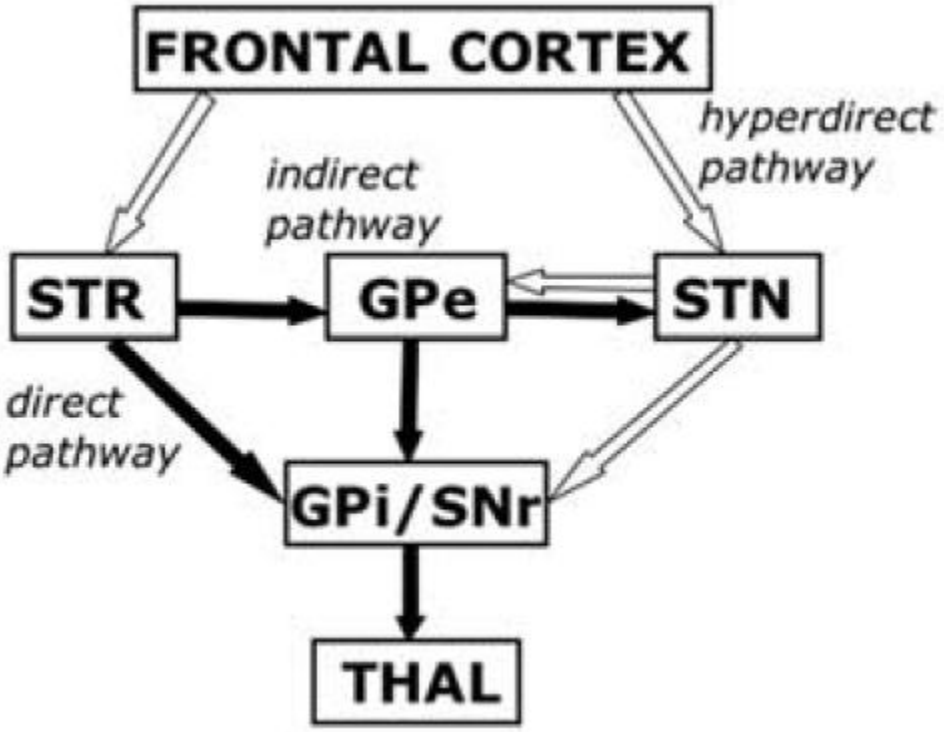
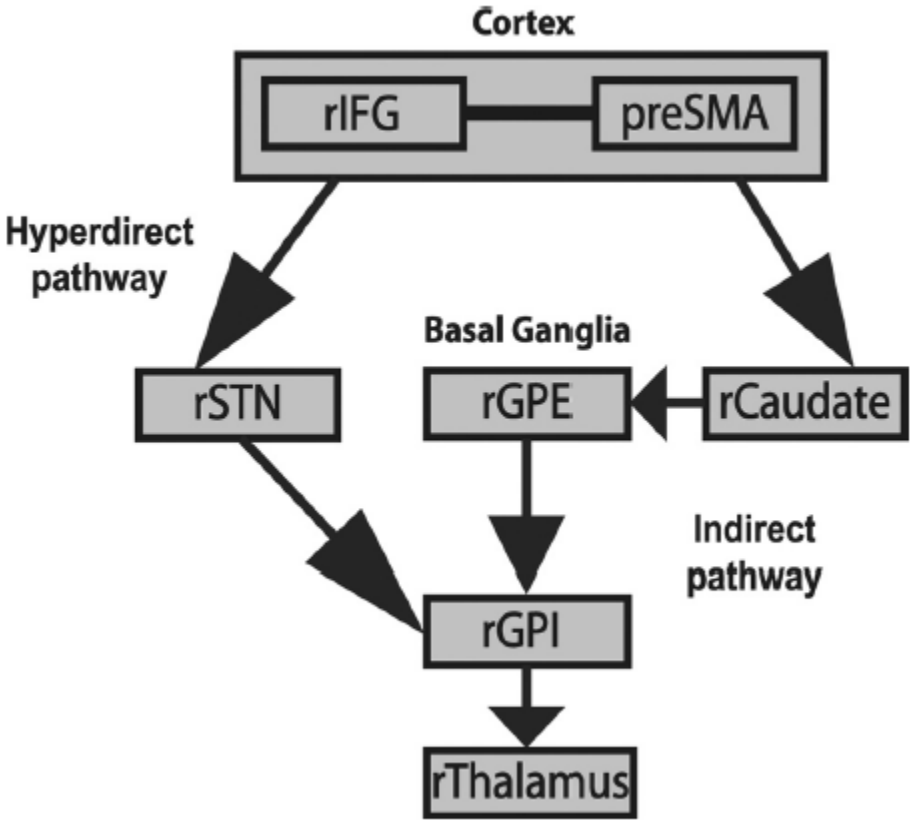


Figure 6: Modified view of the basal ganglia model of response inhibition (Figure from Jahfari et al., 2011).



CHAPTER 2: STUDY 1.0

ASSESSING RESTING STATE FUNCTIONAL CONNECTIVITY AMONG A PUTATIVE RESPONSE INHIBITION NETWORK AND TO ASSESS ITS RELATIONSHIP TO ON THE SST IN PEOPLE WITH SCHIZOPHRENIA

Abstract

Background. Deficits in response inhibition are a prominent feature of schizophrenia (SZ). The right inferior frontal gyrus (rIFG), pre supplementary motor area (pre-SMA), the subthalamic nucleus (STN), the striatum (ST), the globus pallidus (GP) and the thalamus (Thal) have been shown to be recruited in a response inhibition task, the stop signal task and can be conceptualized as forming a putative response inhibition network. **Methods.** 26 healthy controls and 26 age and sex matched patients with SZ performed a stop signal task to assess response inhibition and underwent a six-minute resting state scan to assess functional connectivity at rest. Patients were further categorized into inpatient and outpatient subgroup to assess whether the two groups differed in behavioral performance on the task as well as on the extent of functional dysconnectivity. **Results.** Results suggest that people with schizophrenia have reduced functional connectivity among four regions involved in response inhibition when compared to controls, with inpatients exhibiting additional dysconnectivity among region pairs. Although the groups did not differ significantly in the stop signal reaction time, they did exhibit differences in performance on other behavioral measures. **Discussion.** Our results are the first to indicate decreased functional connectivity among region pairs involved in response inhibition in people with SZ and are consistent with reports of widespread dysconnectivity observed in SZ. The observed patterns of dysconnectivity may be related to behavioral performance.

Schizophrenia (SZ) is a psychotic disorder that affects a person's perceptions, thought processes and behavior and generally manifests as hallucinations, delusions, paranoia and disorganized thoughts and behaviors (DSM-IV-TR, 2000). People with SZ also show deficits in response inhibition, manifested as a decreased ability to suppress an already initiated response (Nolan et al., 2011).

Although the causes and mechanisms of SZ are unclear, the dysconnection hypothesis for this disorder, which assumes that symptoms of SZ arise from dysfunctional integration of a distributed network of brain regions, has become popular (Stephan et al., 2009; see Friston (1995) and Stephan et al., (2006) for reviews). Research indicates widespread dysconnectivity between cortical regions such as the frontal, temporal and parietal cortices and subcortical regions such as the basal ganglia and amygdala in SZ (Hill et al., 2004; Honey et al., 2005; Micheloyannis et al., 2006; Liang et al., 2006; Liu et al., 2010; Tu et al., 2010).

Response inhibition can be measured with a stop task, such as the stop signal task (SST), which is based on Logan's (1994) "race" model. Because all forms of response inhibition work against some form of excitation, the processes involved in stopping can be thought of as a race between stop process (inhibition) and go processes (excitation). In a typical version of the SST, participants are presented with a choice reaction time task. This represents the Go condition since the subjects do not have to inhibit their responses. In the Stop condition (e.g., 25% of total conditions), the go signal is followed by a stop signal of some sort. The Go process of the SST can be easily observed whereas the

Stop process cannot be directly measured as it involves an unobservable event (a person performs correctly on the stop task if she correctly stops a response that was already started by the Go process). The SST provides an estimate of the time taken to stop a response, the stop signal reaction time (SSRT), and this serves as the quantifiable behavioral measure of response inhibition.

Studies have identified the right inferior frontal gyrus (rIFG), pre supplementary motor area (pre-SMA; Duann et al., 2009) the right and left globus pallidus (GP; Aron et al., 2006), the right and left thalamus (Thal) and the subthalamic nucleus (STN) as regions recruited during the SST (Aron et al.,2006; Li et al., 2008; Aron et al., 2003). These neural regions served as the regions of interest (ROIs) in the present study.

"RSFC" refers to the significant statistical relationship of the blood-oxygen-level-dependent (BOLD) activity among spatially distinct neural regions under non-task conditions (Friston, 1995). Biswal et al., (1995) showed that the right and left somatomotor cortices significantly correlated in its low frequency spontaneous fluctuations (≤0.1Hz), an observation that has been replicated many times (Cordes et al., 2001; Xiong et al., 1999). By placing seed regions in additional brain areas, or by conducting independent components analyses on resting state data (Beckmann et al., 2006), other neuro-anatomical systems have been shown to be coherent in their spontaneous BOLD activity during rest, including the visual system (Lowe et al., 1998), dorsal and ventral attention systems (Fox et al., 2006), and areas that subserve language (Cordes et al.,

2000; Hampson et al., 2002). An important and consistent finding is that areas with similar functionality—that is, regions that are similarly modulated by various task paradigms—tend to be significantly correlated in their resting state functional connectivity (RSFC) (Fox et al., 2006).

Although deficits in SST performance in people with SZ have been demonstrated (Nolan et al., 2011; Lipszyc, 2010), the underlying neural connections among structures within the putative response inhibition network have not been established. Our current study addresses this gap in the literature by comparing the RSFC among the ROIs comprising the response inhibition network in people with SZ and healthy controls.

METHODS

Subjects

Twenty six people with DSM-IV-TR diagnosis of SZ or schizoaffective (SA) (21 males, 5 females) and twenty six non-psychiatric (17 males, 9 females) age-matched subjects participated in the study (Table 1). Of the twenty six people with SZ or SA disorder, nineteen were inpatients and seven were outpatients (Table 2). Additionally, of the twenty two patients diagnosed with SZ, twelve were subcategorized as undifferentiated, nine as paranoid and one as residual. Four subjects were diagnosed as SA. At the time of the study, all patients were receiving antipsychotic medications (11 on atypical medications only, 1 on typical medication only and 3 on both typical and atypical medication). Medication information was not collected for 11 patients. The study was approved by the NKI Institutional Review Board. All subjects provided voluntary informed consent and

were compensated $10/hour for their participation. At the time of the study, all patients were on antipsychotic medications.

The Structured Clinical Interview for DSM-IV-TR Axis I Disorders Patient edition (SCID-I/P) was administered to patients and the SCID Nonpatient version (SCID-I/NP) was administered to controls by trained raters. Subjects with a DSM-IV Axis I diagnosis other than SZ or SA disorder, including psychotic mood disorder, alcoholism or substance dependence within the past 6 months were excluded from the study, as were subjects with any clinical neurological conditions. Controls as well as outpatients living on the grounds of the Rockland Psychiatric Center (RPC) were recruited from NKI's Volunteer Recruitment Program (VRP). Inpatients were recruited from the two 12-bed research units located at NKI. These units comprise the Clinical Research and Evaluation Facility (CREF) and primarily receive its patients from RPC. We confirmed the absence of drugs of abuse in outpatients and controls by performing urine toxicology screens.

The positive and negative syndrome scale (PANSS) for schizophrenia was also administered to the patients by trained raters and the three subscales, positive, negative and general psychopathology scale.

Procedure

Stop Signal Task

In our version of the stop task, participants are presented with either a letter "X" or a letter "O." They are told to press the right button when the letter "X" is presented and the left button when the letter "O" is presented. These represent the Go stimuli since the subjects are not told to inhibit their responses. In the

Stop stimuli condition (25% of trials), the letter “X” or “O” is followed by a red square (see Figure 1).

The time between the presentation of the “X” stimulus and the “O” stimulus, the SSD, was dynamically changed from 250 ms to 750 ms in accordance with the subject’s performance, such that when the subject correctly withheld a response during the stop trial, the SSD increased by 50 ms, up to a maximum SSD value of 750ms. Alternatively, if the subject responded incorrectly to a stop trial, then the SSD decreased by 50 ms, down to a minimum SSD value of 250ms. These adjustments were made on the assumption that dynamically varying the SSD would yield a p(inhibit) of 50% and that as SSD increases, the subject is more likely to respond during a stop condition and vice versa. This assumption is the key to understanding the inhibition function and how SSRT can be calculated.

In addition to the SSRT measure, SST can be used to calculate go and stop accuracy. Go accuracy is calculated as:

$$\frac{\text{\# Correct Go Trials}}{\text{Total \# of Go Trials}}$$

I argue for and utilize an alternate method of stop accuracy calculation. In this method, correct stop trials (the value in the numerator) is defined as those correct stop trials that are preceded by a go trial in which the subject responded. In this way, we can eliminate stop trials during which the subject is not involved in response inhibition but is rather is idly sitting. Therefore, in these cases, although the subject responds correctly to a stop trial (because she didn’t press a button),

I argue that inclusion of these trials biases the results towards increase inhibition. However, by only including those stop trials that are immediately preceded by a go trial in which the subject responded, we can decrease the likelihood of irrelevant trials and thus ensure that we are actually testing that which we seek to test.

$$\frac{\text{\# Correct Stop Trials}}{\text{Total \# of Stop Trials}}$$

MRI Image Acquisition

The study was performed on a 3.0 Tesla Siemens Tim Trio system (Erlangen, Germany) housed in the Center for Advanced Brain Imaging at NKI. Head stabilization was achieved using cushions and all subjects wore ear plugs to attenuate noise. Because of possible effects of sedatives on functional connectivity (Kerssens et al., 2005), patients were not tested on any measure within 8 hours of the administration of a PRN medication. All subjects underwent an MRI scan where manual shimming procedures were performed and scout images were acquired. A six minute resting state MRI scan was also acquired. Before the six minute resting state scan, all subjects were instructed to lie still with their eyes closed and stay awake.

Image sequence acquisition:

Subjects were scanned using a six minute echo planar imaging (EPI) sequence (TR = 2sec, TE = 30ms, FOV = 240mm, matrix = 96^2, 34 2.8 mm slices, IPAT = 2). The first five volumes are discarded to allow for T1-relaxation. A magnetization prepared acquisition of a gradient echo (MPRAGE; TR = 2500 ms, TE = 3.5 ms, flip angle = 8 deg, effective TI = 1200 ms, 256 x 256 matrix, FOV =

256 mm, NEX = 1, 192 slices, 1 mm slice thickness, 0 mm skip) was acquired for image registration and segmentation.

Image pre-processing

BOLD images were converted into NIFTI format. Resting state data were preprocessed using scripts from the 1000 Functional Connectomes project (http://www.nitrc.org/projects/fcon_1000/; Biswal et al., 2010). These scripts motion corrected the data, smoothed using a Gaussian kernel of 5 mm full-width at half-maximum (FWHM), band-passed, scaled, and detrended the 4D time series.

The FCONN scripts also skullstripped and segmented the MPRAGE using FMRIB Software Library's (FSL's) FMRIB's automated segmentation tool (FAST) program. Segmented images along with the ROI images were transformed to 2x2x2 mm^3Montreal Neurological Institute (MNI) space using FSL's FMRIB's Linear Registration Tool (FLIRT) program. The WM and CSF images, as well as the global image were used as masks to extract time series for each of these compartments along with the motion parameters obtained from Analysis of Functional NeuroImage (AFNI) to remove spurious sources of variance. The preprocessed 4D time series were then residualized for these covariates of no interest using FSL's fMRI Expert Analysis Tool (FEAT) program. Time series data for each ROI were extracted from these residualized data and retained for correlation analysis. Temporal filtering between 0.01Hz and 0.1Hz was also done.

RSFC analysis

To determine the RSFC between our ROIs, we assessed BOLD signal in rIFG, STN, GP, ST, preSMA and the Thal. We followed Aron and Poldrack (2006) and placed an STN seed at [10, -15, -5] and preSMA seed at [6, 20, 50]. The seeds for GP, Thal and rIFG were placed according to the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). The time series for each ROI were extracted from the residualized data and then correlated with the other ROIs after the pre-processed 4D (e.g., rGP with rIFG). We converted these correlations to Z-scores using Fisher's *r*-to-z transformation (Vincent et al., 2006). Correlations were performed on the (demeaned) time series data to provide FC between seeds.

Post-Hoc Statistical Analysis

We conducted a post-hoc comparison using Tukey's test to assess differences in RSFC among patient subgroups (inpatients and outpatients) and healthy controls.

Multiple Regression Analysis

We used multiple regression analysis to determine whether RSFC can be used to predict inhibitory performance on the SST, as measured by SSRT. Because multiple regression analysis makes a number of assumptions[2], we tested for these assumptions in both subject groups.

[2] Multiple regression makes a number of assumptions about the data and is not forgiving if those assumptions are violated. The assumptions include lack of outliers, normal distribution and multicollinearity. "Multicollinearity" refers to the presence of correlations among the variables. Ideally, the independent variables (IVs) should show at least some correlation amongst one another, not to exceed r = 0.9. Additionally, the IVs should be correlated with the dependent variables, preferably above r = 0.3 (Fields, 2005). Both the "Tolerance" as well as "VIF" values

RESULTS

Behavioral Results

Mean go accuracy, stop accuracy (StopACC), go reaction time (GoRT) and SSRT were computed for all subjects. An independent samples t-test revealed no significant between group difference among controls *M*=666.06 ms, *SD*=88.58 and patients *M*=668.53 ms, *SD*=90.71 on go reaction time, t(50)=0.10, p=0.92. Additionally, there was no significant between group difference between controls *M*=109.47 ms, *SD*=93.15 and patients *M*=122.65 ms, *SD*= 109.14 on SSRT, t(50)=0.47, p=0.64. However, results indicated a significant between group difference among controls *M*=85.82 %, *SD*=13.20 and patients *M*=71.46 %,*SD*=22.66 on go accuracy, t(50)=2.80, p=0.007. Similarly, results indicated a significant between group difference among controls *M*=54.80 %, *SD*=11.03 and patients *M*=48.08 %, *SD*=11.4 on stop accuracy, t(50)=2.1, p=0.047 (see Table 3).

To assess differences in the pattern of impairment among patient subgroups, we analyzed the behavioral data for inpatients and outpatients and we conducted a one-way ANOVA (See Table 4).

One-way ANOVA did not yield significant results for go reaction time: F (2,49)=0.72, p=0.492 or for SSRT: F(2, 49)=0.123, p=0.88. However, analysis yielded significant between group differences on go accuracy (GoACC) F(2,49)=5.94, p=0.005 and stop accuracy F(2,49)=3.66, p=0.03(See Table 5).

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should be calculated to determine the presence of multicollinearity that may be missed by correlational analysis alone. In order for a particular IV to be included in further analysis, tolerance value should be greater than 0.1 whereas VIF value should not exceed a value of 10. Data that violate any assumptions are to discarded from further analysis.

Tukey's post hoc tests revealed that the significant group difference observed in go accuracy was present between controls *M*=85.82 %, *SD*=13.20 and inpatients *M*=67.34 %, *SD*= 23.75, p=0.004 but not between controls *M*=85.82 %, *SD*=13.20 and outpatients, *M*=82.64 %, *SD*=15.71, p=0.91. Similarly, Tukey's post hoc tests revealed that the significant difference observed in stop accuracy was present between controls *M*=54.80 %, *SD*=11.03 and inpatients *M*=45.89 %, *SD*=11.03, p=0.032 and not between controls *M*=54.80 %, *SD*=11.03 and outpatients *M*=54.03 %, *SD*= 10.97, p=0.97.

Interregional correlations

A one-way repeated measure ANOVA using ROI pairs as a Within-subjects factor and Group (patients, controls) as a Between-subjects factor was conducted. Results indicate a significant between-subjects effect for group (F=13.27, p<0.001, partial eta squared=0.21). Results indicated a significant Region x Group effect (F=2.16, p=0.026, partial eta squared=0.58).

In a follow up analysis, for each subject, we computed twenty nine pairwise correlations among the predetermined ROIs. We then tested for group differences between patients and controls using independent sample t-tests. The alpha level was Bonferroni corrected for alpha inflation by setting p=0.05/29 (=0.002).

Four region pairs showed a between-group difference in the strength of RSFC (See Figure 2), with controls exhibiting significantly higher connectivity than patients: (R)STN-(L)Thal (t(50)= 3.981, p=0.0005)(controls: *M*=0.39, *SE*=0.03;patients: M=0.18, SE=0.03); (L)Thal-(R)GP (t(50)=3.734, p=0.0005)

(controls: *M*=0.33, *SE*=0.03; patients: *M=0.13, SE*=0.04) , (R)STN-(R)GP (t(50)=3.455, p=0.001) (controls: *M*=0.29, *SE*=0.03; patients: *M*=0.11, *SE=0.03)*and (R)GP-(L) ST (t(50)=4.400, p=0.0005) (controls: *M*=0.43, *SE*=0.03; patients: *M=0.2, SE*=0.03). These results indicate a significant between-group difference among resting state connectivity among neural regions implicated in response inhibition (Tables 6).

Studies have shown a marked difference in social and cognitive functioning as well as severity of symptoms among inpatients and those treated in outpatient clinics (Knobler et al., 1999; Perlick et al., 1992). Further, functional connectivity at rest between bilateral frontal lobes has been shown to be related to psychotic symptoms (Rotarska-Jagiela et al., 2010). However, to our knowledge, no studies to date have assessed functional connectivity patterns within a putative response inhibition structures in patient subgroups. As such, in order to assess whether there is a differential pattern of RSFC among patient groups, we conducted a one-way ANOVA.

Results indicate a significant between group difference among the four regions pairs described earlier: (L)ST-(R)GP, $F(2,49)=10.63$, $p=0.0005$, $\eta^2=0.55$; (R)STN-(L)Thal, $F(2,49)=9.114$, $p=0.0005$, $\eta^2= 0.52$, (L)Thal-(R)GP,$F(2,49)=6.965$, $p=0.002$, $\eta^2=0.44$ and (R)STN-(R)GP, $F(2,49)=6.015$, $p=0.005$, $\eta^2=0.43$, where patients show decreased RSFC when compared to controls (Table 7). There were no region pairs where patients exhibited increased RSFC compared to controls.

Post-hoc comparison using Tukey's tests revealed that controls exhibited increased RSFC among all region pairs when compared to patients. However, inpatients (not outpatients) exhibited additional decreased RSFC among two of the region pairs: (L) Thal-(R)GP, t (43)=3.453, p=0.001, r=0.12 and (R)STN-(R)GP, t(43)= 3.23, p=0.002, r=0.1 when compared to controls : (L) Thal-(R)GP, t (43)=3.453, p=0.001, r=0.33, (R)STN-(R)GP, t(43)= 3.23, p=0.002, p=0.29 suggesting that they have additional impaired connectivity in their response inhibition network.

We also assessed the correlation between RSFC and go and stop behavioral measures on the SST in the control population as well as the patient subpopulation. There was no significant correlation between go or stop accuracy and functional connectivity among any of the region pairs. Assessing the patient subpopulation by inpatient and outpatient yielded differences in the pattern of relationship between behavioral performance and the connectivity among structures within the subcortical structures. Stop accuracy measures among the inpatient population yielded two outliers and were subsequently removed from the analysis (See Figure 3). Among the structures that exhibited decreased functional connectivity in the inpatient population, (L)ST-GP showed a significant correlation with stop accuracy, r=0.58, p=0.05 (See Figure 5). Outpatient population did not exhibit a significant correlation between the impaired connectivity pairs and any behavioral measures.

Medication information was collected for 15 of the 26 subjects and was converted to chlorpromazine equivalent scores for the available subjects (Woods

et al., 2003). Medication information was missing for 11 patients. Correlation analysis indicated no significant relationship between chlorpromazine medications and RSFC among (R)STN-(L)Thal, r=-0.2, p=0.08. However, a significant correlation was found between medication and (L)Thal-(R)GP, r=-0.54, p=0.0005 and (L)ST-(R)GP, r=-0.26, p=0.12. So, a higher dose of medication is associated with decreased functional connectivity (see Table 8).

Multiple Regression analysis--Behavior

The dependent variable (DV) of SSRT was computed for all subjects. A one-way ANOVA did not yield significant between group differences for SSRT $F(2)=0.022$, $p=0.88$, $\eta^2 = 0.03$. Therefore, SSRT was not entered into the regression analysis.

DISCUSSION

The primary finding of this study is that people with schizophrenia exhibit decreased RSFC among neural structures that have been shown to be recruited in response inhibition tasks, particularly, the stop signal task. These finding are the first to examine RSFC among structures implicated in response inhibition in schizophrenia and lend further support to the dysconnection hypothesis postulated by Stephan et al. (2006) as a model to explain the symptoms observed in SZ.

Our study shows that patients overall exhibit decreased connectivity patterns when compared to controls. However, the patient subpopulations show differential patterns of dysconnectivity: although both outpatients and inpatients exhibited dysconnectivity among subcortical structures involved in both direct and indirect pathway of the basal ganglia model of response inhibition, inpatients

showed additional connectivity problems among subcortical structures: ST, STN, GP and Thal. Impaired connectivity among the affected structures suggests that the net result is increased activity of the premotor regions by the Thal as a result of decreased inhibition by the GP. As such, based on these dysconnectivity patterns, we would expect to see decreased inhibition during the stop trials. Indeed, inpatients show a positive correlation among the FC between ST and GP and stop accuracy. This observation suggests that as the extent of FC among the ST and GP decreases, so does performance on the stop accuracy component of the SST because of decreased inhibition of the GP by the ST, resulting in a net excitation the thalamus and the premotor regions.

However, use of the adaptive algorithm (recall, that the SSD was dynamically modified as a result of each subject's performance on the stop component of the SST) confounds the value of the stop accuracy and makes any between group differences on this measure virtually un-interpretable for a number of reasons:

First, according to the horse-race model, as the SSD increases, the p(inhibit|signal) decreases and subjects are more likely to incorrectly respond to the stop stimuli. However, our results indicate otherwise. Both controls and patients showed an increase in stop accuracy above a SSD of 550 ms when compared to below an SSD of 550 ms, suggesting that both group performed better at longer SSDs. This improved performance is reflected in the % of SSD above 550 ms. In controls, 79%, SD=+/- 10.1 of all SSDs were above 550 ms whereas 67.47%, SD= +/- 25.9, of all SSD in patients were above 550 ms.

Because the subjects are spending the majority of the time above an SSD of greater than 550 ms (As reflected by the % of SSD above 550 ms) and because their stop performance improves as SSD increases, the task may lack construct validity. This violation of the underlying assumption of the horse-race model makes the resulting stop accuracy measure and the subsequent group comparison invalid.

Additionally, both subject groups showed an increase in go reaction time as a function of SSD, suggesting that they took longer to respond to the go accuracy component of the SST. This increase in go reaction time suggests that the subjects employed a waiting strategy to see if the stop signal would appear before making or withholding a response. This increase in go reaction time might explain the observation of increased stop accuracy on the SST. Thus, the observed differences in stop accuracy may not reflect a true difference on the groups' ability to correctly withhold a response but rather may reflect their ability to adopt a strategy to perform on the task. Leotti and Wager (2010) have found that strategies such as waiting can influence SST performance.

For these reasons, the use of the adaptive algorithm to make inferences about population performance on the stop accuracy measure is not valid

Outpatients did not exhibit any significant correlation among the FC of any of the region pairs and behavioral measures on the SST. This suggests that, the decreased connectivity at rest (and thus, a decreased "baseline readiness" in their ability to recruit these regions) does not impair their ability to adequately recruit these regions in the service of the task. This may be because during the

course of task performance, the outpatients are able to adequately recruit these regions (and thus exhibit normalized connections) and perform as well as their healthy counterparts. To test whether such normalizations occur during task, future studies should aim to assess the connectivity during task performance.

Our results suggest that the pattern of dysconnectivity is not observed among structures that aid in target detection and the subsequently send information to the site of motor response inhibition. Extensive literature suggests that the rIFG is part of the ventral attention system, which activates in response to the detection of a salient target, such as the stop signal in the stop signal task. Studies show that rIFG along with the temporal parietal region responds and reorients attention to an infrequently occurring external stimuli, such as the stop signal. The rIFG responds to a stop signal and expedites the stop process in the preSMA during correctly inhibited stop trials (Duann et al., 2009). Models using effective connectivity measures suggest that once the salient cue, the stop signal, is detected, excitatory, glutamatergic neural activity is sent via projections from the rIFG to the preSMA, the primary site of motor response inhibition. Results from our data show that the connectivity patterns between the rIFG and the preSMA remain intact, suggesting that the observed behavioral deficits may not be attributable to detection of the stop signal. However, it seems that in both patient subpopulations, there is a subsequent breakdown in connectivity among structures once the salient cue is detected by the rIFG and sends excitatory connections to the preSMA.

There are several possible explanations for the observed lack of significant SSRT difference between controls and patients. The version of the SST we used had some design flaws that may have contributed to the observed lack of significant results. First, in direct contrast to the suggestion outlined in Logan (1994), the largest SSD should be set around 600 ms. However, in our version of the SST, the largest SSD was set at 750 ms whereas the largest SSD set in STOP-IT task was 600 ms. This might help explain the increase in Go reaction time observed in both controls and patients as the SSD increased. When we split the data into above and below an SSD of 600 ms, we observed an increase in Go reaction time to the primary task with increased SSD. Below an SSD of 600ms: patients had a mean Go reaction time of *M*= 597.05 ms, *SD*+/-=83.06 and controls had a mean Go reaction time of *M*=608.43 ms, *SD*+/-=78.22 whereas above an SSD of 600 ms, patients had a mean Go reaction time of *M*=651.49 ms, *SD*+/-=98.63 and controls had a mean Go reaction time of *M*=621.80 ms, *SD*+/-=76.99. This increased reaction time suggests that the subjects may have waited after the presentation of the go stimulus to see if the stop stimulus was presented before responding.

In our study, we were not able to use the control and patient subjects' functional connectivity data at rest to predict SSRT due to the data violating multiple assumptions that must be met in order to use multiple regression analysis (Tabachnik & Fidell, 2007; Pallant, 2007).

Similar to our earlier correlation finding, our regression analysis suggest that the RSFC of the region pair (R)ST-(L)GP, both involved in the stopping

process, can be used to predict stop accuracy on the SST in patients. However, for reasons outlined earlier, any inferences made using the stop accuracy behavioral measure should be made cautiously (Aron et al., 2006; Aron et al., 2007; Zandbelt & Vink, 2010).

A major limitation of the study is that all patients were receiving antipsychotic medications at the time of the scanning. A review by Davis et al., (2005) suggested that treatment with antipsychotic medications results in normalization of brain functions, so that it is more similar to the brain functions in controls. However, even if treatment with antipsychotics medications were shown to normalize functional connectivity, the presence of observed differences in RSFC suggests that our results are likely attributable to the disease rather than pharmacological therapy. However, the confounding effects of medication on normalizing functional connectivity cannot be ruled out until future studies with first episode SZ and medication-naïve patients are conducted.

A second major limitation of the study was the possible lack of construct validity of the SST used to make inferences about group differences in the latency of the stop process. For reasons outlined earlier, the task was not designed in adherence to the principles outline in Logan (1984). Future studies that address the concerns listed earlier should be conducted.

In summary, the present finding demonstrates reduced resting state functional connectivity in people with schizophrenia among structures within a putative response inhibition network and is the first such study in schizophrenia

research. In inpatients, this decreased functional connectivity is related to the observed behavioral deficits in the SST, as evidenced by a positive correlation between the FC of ST-GP and the stop accuracy. However, interpretation of this finding must be made cautiously. This finding was not observed in the outpatient population and future studies should explore whether this is related to a normalization of connectivity patterns during task performance. Additionally, because of the differential pattern of dysconnectivity observed within the patient population, future studies should attempt to study these groups independently.

Figure 1: Stop Signal Task. “+” represents fixation point. “X” and “O” represent the go trials where the subject is instructed to respond by pressing the right and left button, respectively. The red box represents the stop trial where the subject is instructed to withhold her response to X and O.

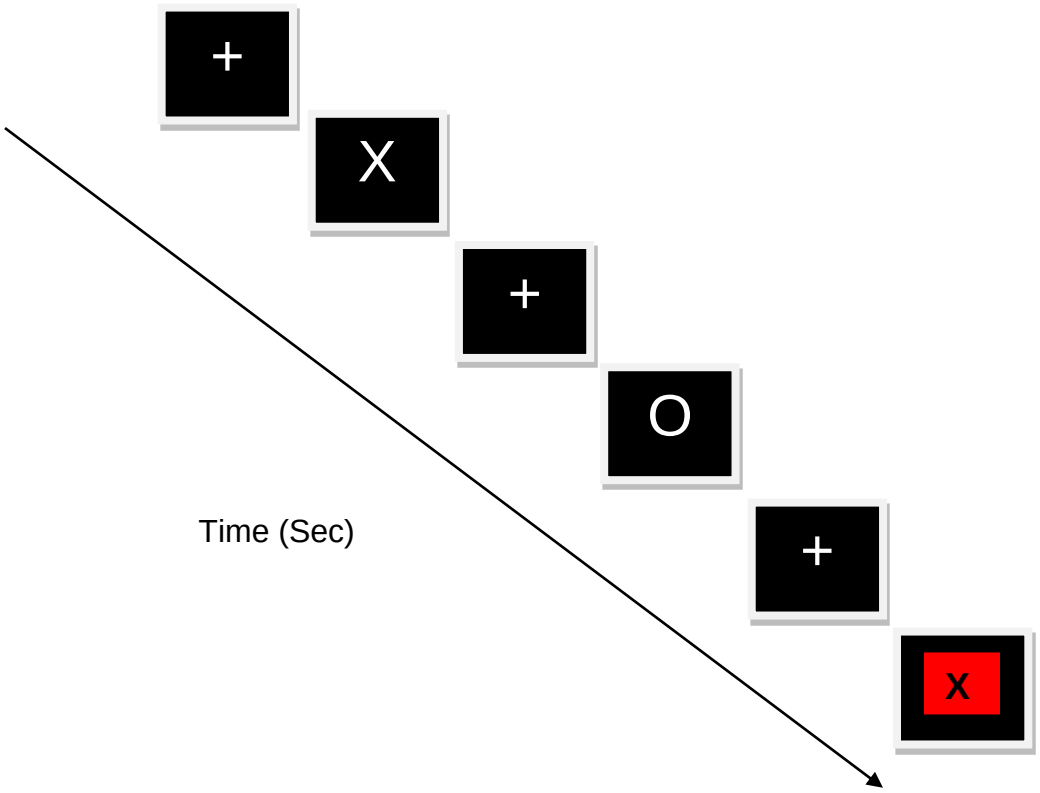
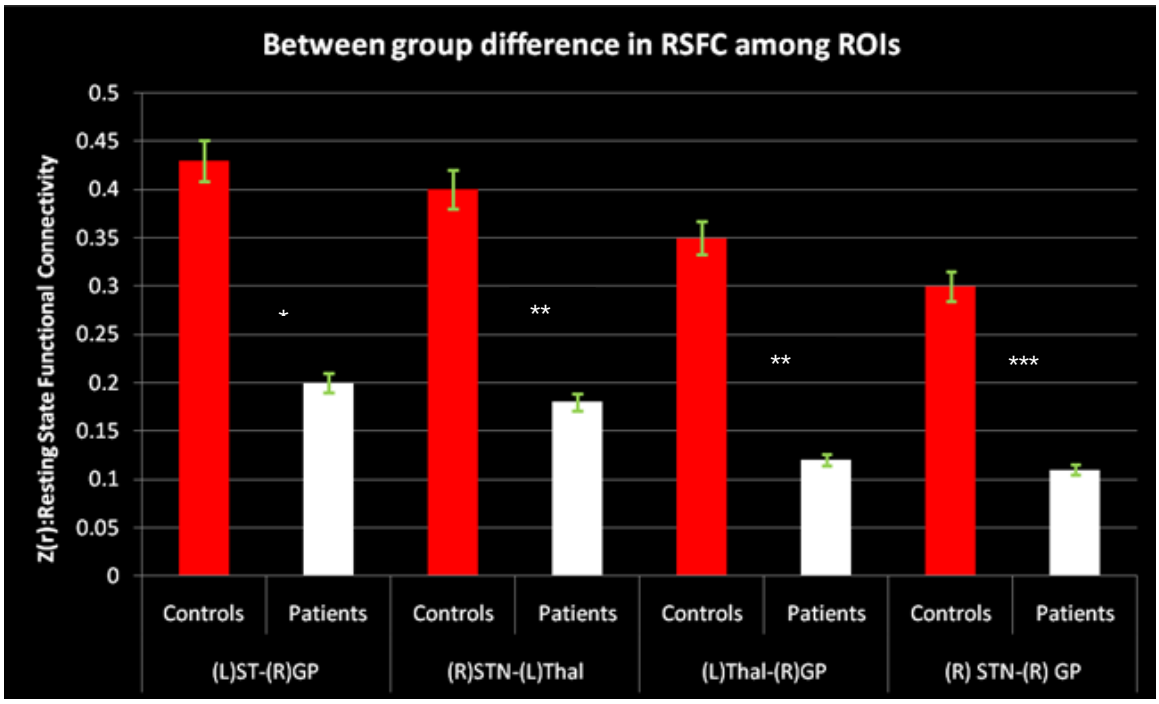


Figure 2: Between group difference in RSFC among healthy controls and patients with SZ or SA



*=significant between group difference, p=0.0005
**=significant between group difference, p=0.0005.
***=significant between group difference, p=0.001.

Figure 3: Stem and leaf diagram of stop accuracy distribution among inpatients with SZ or SA

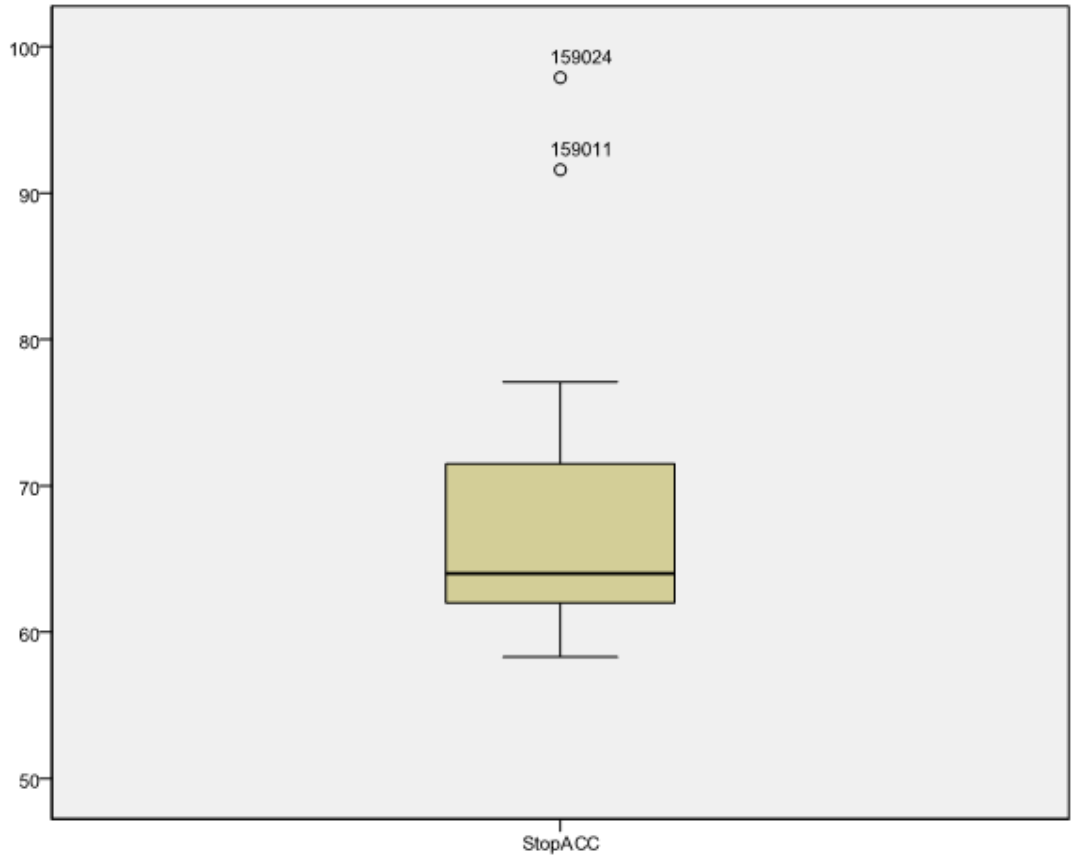


Figure 4: Correlation between stop accuracy and FC between (L)ST-(R)GP in inpatients with SZ or SA

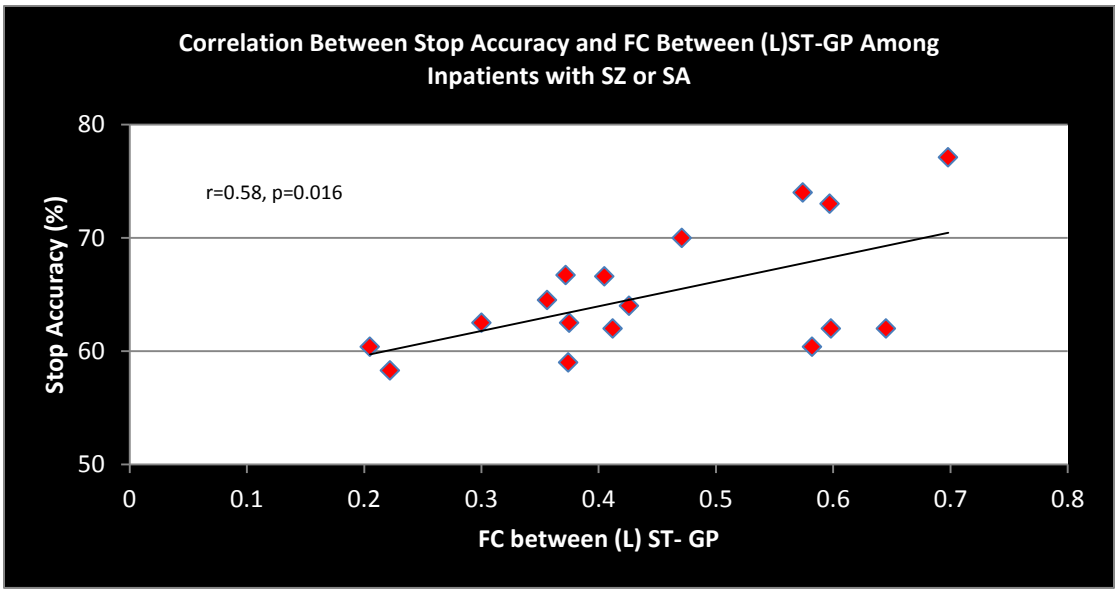


Table1: Demographic profiles of patients with SZ or SA and healthy controls

Characteristics	Patients with SZ or SA (N=26)	Healthy Controls (N=26)	t/χ2 value	p-value
Age (years)	39.23	39.73	0.188	0.85
Sex(M/F)	21/5	19/7	0.74	0.43
Race(White/Black/Other)	8/14/4	10/11/5	0.70	0.76
Diagnosis(SZ/SA)	22/4	N/A	N/A	N/A
Inpatients/Outpatients	19/7	N/A	N/A	N/A

Table 2: PANSS scores by inpatient and outpatient subgroups

PANSS Characteristics	Inpatients with SZ or SA (N=11)	Outpatients with SZ or SA (N=7)	T-Value	p-value
Positive Mean Score	21.36	15.43	2.22	0.041
Negative Mean Score	20.45	17.57	1.21	0.245
Total Mean Score	78.45	65.29	2.48	0.025

Table 3: Behavioral data from the SST for controls and patients with SZ or SA

Subject Group	Mean Go Accuracy (%)	SD	SE	Mean Stop (%)	SD	SE	Mean SSRT (ms)	SD	SE	Mean GoRT (ms)	SD	SE
Healthy Controls (N=26)	85.82	13.2	2.59	54.8	11.03	2.3	109.47	93.15	18.27	666.06	88.58	17.37
Patients with SZ or SA (N=26)	71.46	22.66	4.44	48.08	11.4	2.2	122.65	109.14	21.4	668.53	90.71	17.19

Table 4: Behavioral data from the SST for inpatients and outpatients with SZ or SA

Subject Group	Mean Go Accuracy (%)	SD	SE	Mean Stop (%)	SD	SE	Mean SSRT (ms)	SD	SE	Mean GoRT (ms)	SD	SE
Inpatients (N=19)	67.34	23.75	5.42	45.89	11.03	2.53	124.82	113.67	26.08	681.24	64.3	14.75
Outpatients (N=7)	82.64	15.71	5.94	54.03	10.97	4.15	116.76	103.99	39.31	634.03	141.36	53.43

Table 5: Between group difference on behavioral measures on the SST among controls and patients with SZ or SA using one way ANOVA

Behavioral measure	F-value	p-value	η^2
Go accuracy	5.941	0.005	0.8
Go reaction time	0.72	0.492	0.97
Stop accuracy	3.66	0.03	0.86
SSRT	0.123	0.884	0.99

Table 6: Between group difference in mean RSFC among healthy controls and people with SZ or SA

ROI Pairs	Patients (N=26)	Healthy Controls (N=26)	t-value	p-value
(R) STN-(L) Thal	0.39	0.18	3.9	0.0005
(L) Thal- (R) GP	0.33	0.13	3.7	0.0005
(R) STN- (R) GP	0.29	0.11	3.5	0.001
(R) GP- (L) ST	0.43	0.2	4.4	0.0005

Table 7: Between group difference in RSFC among controls, inpatients and outpatients using one-way ANOVA

ROI pairs	F-value	p-value	η^2-value
(R) STN-(L) Thal	9.11	0.0005	0.52
(L) Thal-(R) GP	6.97	0.002	0.44
(R) STN-(R) GP	6.01	0.005	0.43
(R) GP-(L) ST	10.63	0.0005	0.55

Table 8: Correlations between antipsychotic medications and RSFC for patients with SZ or SA

ROI pairs	r-value	p-value
(R) STN-(L) Thal	-0.2	0.08
(L) Thal-(R) GP	-0.54	0.0005
(R) STN-(R) GP	-0.59	0.0005
(R) GP-(L) ST	-0.26	0.12

*=At the time of analysis, medication data were missing for 11 subjects

CHAPTER 3: STUDY 2.0

ASSESSING THE RELATIONSHIP BETWEEN BEHAVIORAL PERFORMANCE ON THE SST AND TBFC AMONG STRUCTURES IN A PUTATIVE RESPONSE INHIBITION NETWORK IN PEOPLE WITH SCHIZOPHRENIA

Abstract

Background. Deficits in response inhibition are a prominent feature of schizophrenia (SZ). The right inferior frontal gyrus (rIFG), the subthalamic nucleus (STN), the globus pallidus (GP) and the thalamus (Thal), the presupplementary motor area(preSMA) and the striatum (ST) have been shown to be recruited in response inhibition tasks and can be conceptualized as forming a putative response inhibition network. Although deficits in response inhibition tasks have been demonstrated, the underlying neural connections have not been explored. Our previous study attempted to address this gap in the literature by assessing the functional connectivity (FC) at rest and the current study furthers the literatures by assessing the functional connectivity during task performance. **Methods.** In order to assess response inhibition, 26 patients with SZ and 26 healthy controls performed the stop signal task in the scanner. These were the same subjects as described in Chapter 2. We calculated the functional connectivity during task performance to assess changes in connectivity as a function of task performance. Patients were further categorized into inpatient and outpatient subgroup to assess whether the two groups differed in behavioral performance on the task as well as on the extent of functional dysconnectivity. **Results.** Although subjects did not differ in the response inhibition behavioral measure of interest, they did differ in other behavioral measures. Further, results indicate a decrease in FC during task performance among people with SZ among response inhibition structures whereas the decreased functional connectivity observed at rest normalized during task performance. **Discussion.** Results indicate that the patient population exhibited decreased connectivity during task performance when compared to controls, with this dysconnectivity observed only among the inpatient population. This may suggest that this dysconnectivity observed among the inpatients may be indicative of increased symptomotology. Additionally, the observation of a complete normalization of functional connectivity from rest to during task performance within the outpatient group suggests that they are able to adequately recruit these regions during task performance and thus perform as well as controls.

Response inhibition, the ability to inhibit a response that is no longer task-appropriate, is a hallmark of executive control and has been shown to be impaired in people with SZ (Nolan et al., 2011). The stop-signal paradigm has been extensively used to study response inhibition (Logan 1984). The standard stop-signal paradigm consists of two tasks—the primary task and the secondary task. The primary task requires the fast and accurate completion of reaction time task whereas the secondary task consists of an auditory or a visual signal that, when presented unpredictably, requires the subject to inhibit their response to the primary task. The stop signal task (SST) is often used to study stop signal performance and response inhibition.

Stop Signal Task

The SST, based on Logan's (1984) horse race model, can be conceptualized as a race between the independent "go process" and the "stop process." The go process begins at the onset of the go stimulus and the stop process begins at the onset of the stop process. If the go process finishes before the stop signal process, then a response occurs. If the stop-signal process finishes before the go process, then the behavior is emitted. According to the horse race model, response inhibition is dependent on the relative *finishing* times of the go and stop process, as represented by the vertical line in Figure 1A. The left side of the vertical line represents the times where the go process finished before the stop process and thus the behavior occurred. In contrast, the right side of the vertical line represents the times where the stop process finished

before the go process and thus the behavior did not occur (See Figures 1A and 1B).

The race model helps explain the relationship between the stop signal delay (SSD), or the time between presentations of the go and stop signals, and the probability of inhibiting a response. Specifically, as the SSD decreases, the p(inhibit) increases and p(respond) decreases. Alternatively, as the SSD increases, the p(inhibit) decreases and p(respond) increases. As mentioned earlier, according to the race model, response inhibition depends on the relative *finishing* times of the stopping process and the go process. Thus, the model helps account for the biasing effects of the go reaction time on the relative finishing times of the stopping and the response generation process.

The horse race model also allows us to calculate and make inferences about an unobservable event—the latency of the stopping process, the stop signal reaction time (SSRT) from observable events such as the SSD and the go reaction time. In further support of studies, such as Nolan et al. (2011), we hypothesize that people with SZ will exhibit increased SSRT when compared to their healthy counterparts.

TBFC

Low frequency fluctuations that occur at rest have been shown to continue during task (Fox & Raichle, 2007) and may be related to or influence behavioral performance. Because there is no consistent term used to describe the temporal correlation among regions similarly recruited during task performance, we introduce the term “task-based functional connectivity” (TBFC) to describe the

temporal correlation of BOLD signals between structures that are activated in the service of some task.

A number of studies have attempted to assess the effects of TBFC on behavioral performance in people with SZ (Boksman et al. 2005; Honey et al. 2005; Meyer-Lindenberg et al. 2001). Boksman et al., (2005) studied the functional connectivity patterns between the prefrontal cortex (PFC), the thalamus and the left ACC in first-episode patients with SZ during a working memory task. Results implicate reduced temporal correlation among these regions during task with deficits in task performance. Similarly, impaired TBFC was observed between the DLPFC and the PCC in chronically ill patients during performance on an N-back working memory task (Calicott et al. 2000), wherein controls exhibited task-related suppression of the medial prefrontal cortex (MPFC) and the posterior cingulate cortex (PCC), whereas patients exhibited decreased suppression of these regions. The magnitudes of connectivity among these regions during rest and during task correlated with psychopathology in patients with SZ (Raichle et al., 2001).[3]

TBFC can also be assessed as a function of task condition, in an fMRI functional connectivity analysis known as psychophysiological interaction (PPI). PPI gives information about task specific increases in functional connectivity

[3]The default mode network (DMN, also known as the task negative network (TNN) refers to a set of structures that are more active at rest than during task. The DMN is comprised of the medial prefrontal cortex, the posterior cingulate cortex, the medial temporal cortex, the precuneus and the medial, lateral and inferior parietal cortex. The DMN is absent is infants but becomes “online” in childhood, thus suggesting that the network undergoes developmental evolution (Broyd et al., 2009). Additionally, the structures of the DMN become disengaged during task performance(Fox et al., 2005)and the extent of such disentangling may be related to behavioral performance.

among areas (Friston et al., 1994; Friston et al., 1997; Gitelman et al., 2003).Duann et al., (2009) showed that the connection between the rIFG and the preSMA increased during correct stop trials when compared to incorrect stop trials, thus suggesting that the connections between the two regions mediate stop accuracy performance on the SST.

Based on this, we made several predictions. We hypothesized that people with SZ would exhibit overall decreased TBFC among structures involved in the SST when compared to controls. Further, we predicted that PPI analysis would show increased functional connectivity between the rIFG and the preSMA during stop minus incorrect stop trials in both patients and controls but that controls would exhibit significantly increased functional connectivity as compared to patients.

Finally, we hypothesized that the degree of functional connectivity during task conditions would be correlated with behavioral performance. Specifically, we hypothesized that people with SZ would show decreased TBFC and this decrease would be correlated with decreased response inhibition on the stop signal task, as determined by the SSRT.

METHODS

Subjects

Twenty six people with DSM-IV-TR diagnosis of SZ or schizoaffective (SA) (N=4) and twenty six non-psychiatric age-matched subjects participated in the study (Table 1). The study was approved by the NKI Institutional Review Board. All subjects provided voluntary informed consent and were compensated $10/hour

for their participation. At the time of the study, all patients were on antipsychotic medications.

The Structured Clinical Interview for DSM-IV-TR Axis I Disorders Patient edition (SCID-I/P) was administered to patients and the SCID Nonpatient version (SCID-I/NP) was administered to controls by trained raters. Subjects with a major DSM-IV Axis I diagnosis other than SZ or SA disorder, including psychotic mood disorder, alcoholism or substance dependence within the past 6 months were excluded from the study, as were subjects with any clinical neurological conditions as well as loss of consciousness. Controls as well as outpatients living on the grounds of the Rockland Psychiatric Center (RPC) were recruited from NKI's Volunteer Recruitment Program (VRP). Inpatients were recruited from the two 12-bed research units located at NKI. These units comprise the Clinical Research and Evaluation Facility (CREF) and primarily receive its patients from RPC. We confirmed the absence of drugs of abuse in outpatients and controls by performing urine toxicology screens.

Procedure

Stop Signal Task

In our version of the stop task, participants are presented with either a letter "X" or a letter "O." They are told to press the right button when the letter "X" is presented and the left button when the letter "O" is presented. These represent the Go stimuli since the subjects are not told to inhibit their responses. In the Stop stimuli condition (25% of trials), the letter "X" or "O" is followed by a red square (See Figure 2).

The time between the presentation of the “X” stimulus and the “O” stimulus, the SSD, was dynamically changed from 250 ms to 750 ms such that when the subject correctly withholds a response during the stop trial, the SSD increased by 50 ms, up to a maximum SSD value of 750ms. Alternatively, if the subject responded incorrectly to a stop trial, then the SSD decreased by 50 ms, down to a minimum SSD value of 250ms. These adjustments were made on the assumption that dynamically varying the SSD would yield a p(inhibit) of 50% and that as SSD increases, the subject is more likely to respond during a stop condition and vice versa. This assumption is the key to understanding the inhibition function (see Figure 1b) and how SSRT is calculated.

According to the suggestion outlined in Logan (1994), the largest SSD should be set around 600 ms. However, in our version of the SST, the largest SSD was set at 750 ms whereas the largest SSD set in STOP-IT task was 600 ms.

In addition to calculating SSRT and go reaction time, SST can be used to calculate both go and stop accuracy. Go accuracy is calculated as:

$$\frac{\text{\# Correct Go Trials}}{\text{Total \# of Go Trials}}$$

I argue for and utilize an alternate method of calculation. In this method, correct stop trials (the value in the numerator) is defined as those correct stop trials that are preceded by a go trial in which the subject responded. In this way, we can eliminate stop trials during which the subject is not involved in response inhibition but is rather is idly sitting. Therefore, in these cases, although the

subject responds correctly to a stop trial (because she did not press a button), I argue that inclusion of these trials biases the results towards increase inhibition. However, by only including those stop trials that are immediately preceded by a go trial in which the subject responded we can decrease the likelihood of irrelevant trials and thus ensure that we are actually testing that which we seek to test.

$$\frac{\text{\# Correct Stop Trials}}{\text{Total \# of Stop Trials}}$$

MRI Image Acquisition

The study was performed on a 3.0 Tesla Siemens Tim Trio system (Erlangen, Germany) housed in the Center for Advanced Brain Imaging at NKI. Head stabilization was achieved using cushions and all subjects wore ear plugs and head phones to attenuate noise.

Because of possible effects of sedatives (Kerssens et al., 2008) on functional connectivity, patients were not tested on any measure within 6 hours of the administration of a PRN medication. All subjects underwent an MRI scan in which manual shimming procedures were performed and scout images were acquired.

The following sequences were acquired:

A 3 plane localizer sequences was acquired along with other sequences:

MPRAGE: TR = 2530 ms, TE = 3.5ms, Flip angle = 8, TI = 1200ms, matrix = 256x256, 192 slices, 1mm thickness, no gap.

Stop Signal Task: TR = 2.55sec, TR = 30ms, matrix=96x96, FOV = 240mm, 34 slices, 2.8 mm thickness, NEX=124 (x 2 blocks), 0.7mm gap, IPAT= 2 (10.3min x 2 blocks of 124 volumes).

MRI Image preprocessing, processing and analysis

BOLD images were converted into NIFTI format using dcm2nii (http://www.cabiatl.com/mricro/). The first 5 volumes were discarded to allow for T1-relaxation effects. Images were skull stripped, motion-corrected, and smoothed using a Gaussian kernel of 5 mm full-width at half-maximum.

The structural scans were segmented into gray matter, white matter (WM) and cerebrospinal fluid (CSF) using FMRIB Software Library's (FSL's) FMRIB's automated segmentation tool (FAST) program. The segmented images along with the ROI images were placed into Montreal Neurological Institute (MNI) space using FSL's FMRIB's Linear Registration Tool (FLIRT) program. The WM and CSF segment images, as well as the global mask were co-registered to standard space and used as covariates of no interest along with the motion parameters obtained from Analysis of Functional NeuroImage (AFNI; Cox 1996) to remove spurious sources of variance.

The time series were then residualized for the covariates of no interest using FLS's fMRI Expert Analysis Tool (FEAT) program. Time series data for each ROI were extracted from these residualized data and retained for correlation analysis.

We followed Aron and Poldrack (2006) and placed an STN seed at [10, -15, -5] and a preSMA seed at [6, 20, 50]. The seeds rIFG and bilateral GP, Thal

and striatum and was placed according to the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), as was done in Aron and Poldrack (2006). The time series for each seed were extracted from the residualized data. Additionally, pairwise correlational analysis were conducted among structures within the putative response inhibition network.

Finally, because studies such as Wardak et al., (2011) showed that the role of the preSMA in inhibitory control is potentially confounded by processes related to movement preparation and that preSMA activation was sustained for several seconds *before* actual motor movement, and because the task conditions introduce their own BOLD responses, we regressed out the movement preparation by entering behavioral data (go and stop accuracy as well as go and stop inaccuracy) entered into the regression model (i.e., three column vectors) as described in Gitelman et al., (2003).Results from this regression analysis were entered to the functional connectivity analysis.

Post-Hoc Statistical Analysis

Studies have shown a marked difference in social and cognitive functioning as well as severity of symptoms among inpatients and outpatients (Knobler et al., 1999) and may impact the neural connectivity. To date, no studies that have assessed the TBFC among structures involved in response inhibition in the SST as a function of patient subgroups. We conducted a post-hoc comparison using Tukey's test to assess differences in TBFC among patient subgroups (inpatients and outpatients) and healthy controls.

Psychophysiological Interaction (PPI)

fMRI images were skull stripped, motion-corrected, and smoothed using a Gaussian kernel of 5 mm full-width at half-maximum (FWHM). Nuisance variables, such as motion, CSF and white matter time series were removed from the data. The seed for rIFG was placed according to the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and the time series for that region was extracted and used as the physiological variable in FEAT.

The averaged time series in the rIFG was extracted to generate the neuronal signal and used as the physiological variable (i.e., three column vector) in the PPI. The psychological variable of interest was the contrast between correct stop and incorrect stop trials. This regressor was convolved with the canonical HRF and entered into the regression model (i.e., three column vectors) as described in Gitelman et al., (2003).

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) with regressors for the task (as the psychological variable), time series from the region of interest (physiological variable), and the interaction (interaction variable) between the task and the region of interest. The PPI analysis was performed for each subject, and the resulting images of contrast estimates on the interaction effect were entered into a random effect between-group analysis. Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann 2003, Woolrich 2004, Woolrich 2008). Z (Gaussianised T/F) statistic images were thresholded

using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of p=0.05 (Worsley 2001).

Multiple Regression Analysis

We used multiple regression analysis to determine whether TBFC measures can be used to predict inhibitory performance on the SST, as measured by SSRT. Because multiple regression analysis makes a number of assumptions[4], we tested for these assumptions in both subject groups. However, SSRT was not retained for further analysis because it did not yield a significant group difference.

RESULTS

TBFC Results

Behavioral measures (go accuracy, stop accuracy, go inaccuracy, stop inaccuracy), convolved with a canonical gama hemodynamic response function, were regressed out to control for motor preparedness and we calculated the four behavioral measures for each subject. However, five controls and 3 patients (2 inpatients, 1 outpatient) did not have enough data points in one or more of the behavioral measure and thus were not entered into further analysis.

Independent samples t-test revealed no significant between group differences in TBFC among any of the regions pairs. However, three region pairs showed significant between group differences when not corrected for multiple

[4] Multiple regression makes a number of assumptions about the data and is not forgiving if those assumptions are violated. The assumptions include lack of outliers, normal distribution and multicollinearity. "Multicollinearity" refers to the presence of correlations among the variables. Ideally, the independent variables (IVs) should show at least some correlation amongst one another, not to exceed r = 0.9. Additionally, the IVs should be correlated with the dependent variables, preferably above r = 0.3 (Fields, 2005). Both the "Tolerance" as well as "VIF" values should be calculated to determine the presence of multicollinearity that may be missed by correlational analysis alone. In order for a particular IV to be included in further analysis, tolerance value should be greater than 0.1 whereas VIF value should not exceed a value of 10. Data that violate any assumptions are to discarded from further analysis.

comparisons, (R) preSMA-(R) GP, t(42)=2.16, p=0.037, (R) STN-(L) GP, t(42)=2.07, p=0.04 and (R) STN-(R) GP, t(42)=2.41, p=0.021. Interestingly, the impaired functional connectivity observed in outpatients with SZ among region pairs at rest was no longer significant during task (See Table 2). Recall that outpatients exhibited decreased connection among the (R)STN-(L)Thal and the (L)ST-(R)GP.

Studies have shown a marked difference in social and cognitive functioning as well as severity of symptoms among inpatients and outpatients (Knobler et al., 1999). However, to date, there are no studies that have neither assessed the TBFC among structures involved in response inhibition in the SST nor assessed the dysfunction among patient subgroups. As such, we conducted a one-way ANOVA to assess differential patterns of TBFC. Results indicate no significant between group differences among any regions pairs. However, one region pair showed a trend in significance: (R) STN-(R) Thal, $F(2,42)=3.02$, $p=0.060$, $\eta^2=0.125$ (see Table 3).

Post hoc comparison using Tukey's revealed that the observed difference in TBFC was only seen among inpatients and controls and not among outpatients and controls. Inpatients exhibited a decrease in TBFC within (R) STN-(R) Thal when compared to controls, $t(37)=2.43$, $p=0.02$. This difference in TBFC was not observed between controls and outpatients, $t(26)=0.41$, $p=0.69$, (See Table 4 and Figure 3).

Behavioral Results

Mean go accuracy, stop accuracy (StopACC), go reaction time (GoRT) and SSRT were computed for all subjects. An independent samples t-test revealed no significant between group difference among controls *M*=666.06 ms, *SD*=88.58 and patients *M*=668.53 ms, *SD*=90.71 on go reaction time, t(50)=0.10, p=0.92. Additionally, there was no significant between group difference between controls *M*=109.47 ms, *SD*=93.15 and patients *M*=122.65 ms, *SD*= 109.14 on SSRT, t(50)=0.47, p=0.64. However, results indicated a significant between group difference among controls *M*=85.82 ms, *SD*=13.20 and patients *M*=71.46 ms, *SD*=22.66 on go accuracy, t(50)=2.80, p=0.007. Similarly, results indicated a significant between group difference among controls *M*=54.80 ms, *SD*=11.03 and patients *M*=48.08 ms, *SD*=11.4 on stop accuracy, t(50)=2.1, p=0.047. See Table 5.

To assess differential patterns of impairment among patient subgroups, we analyzed the behavioral data for inpatients and outpatients and we conducted a one-way ANOVA (See Table 6).

One-way ANOVA did not yield significant results for go reaction time: F (2,49)=0.72, p=0.492 or for SSRT: F(2, 49)=0.123, p=0.88. However, analysis yielded significant between group differences on go accuracy (GoACC) F(2,49)=5.94, p=0.005 and stop accuracy F(2,49)=3.66, p=0.03(See Table 7).Tukey's post hoc tests revealed that the significant group difference observed in go accuracy was present between controls *M*=85.82 %, *SD*=13.20 and inpatients *M*=67.34 %, *SD*= 23.75, p=0.004 but not between controls *M*=85.82 %, *SD*=13.20 and outpatients, *M*=82.64 %, *SD*=15.71, p=0.91. Similarly, Tukey's

post hoc tests revealed that the significant difference observed in stop accuracy was present between controls *M*=54.80 %, *SD*=11.03 and inpatients *M*=45.89 %, *SD*=11.03, p=0.032 and not between controls *M*=54.80 %, *SD*=11.03 and outpatients *M*=54.03 %, *SD*= 10.97, p=0.97 (See Figures 4A and 4B).

We also assessed the correlation between TBFC and behavioral measures on the SST. Inpatients showed significant correlation between the go accuracy and (L)GP-(L)Thal, r=-0.53, p=0.05 (See Figure 5).

Outpatient population also showed a significant correlation between performance on the stop accuracy and FC among (L)Thal-(R)IFG, r=-0.95, p=0.01 and (R)STN-(L)Thal, r=-0.89, p=0.05. However, these findings were once again skewed by the presence of a singular outlier (See Figure 6). Removal of this outlier resulted in a non-significant correlation between stop accuracy measure and FC among either region pairs.

PPI Results

PPI analysis was conducted for both stop correct and stop incorrect conditions to determine which neural areas would exhibit increased connectivity with the (R) IFG as a function of change in task condition.

Controls:

When selecting the (R) IFG as the seed region, with regards to the within group (controls) PPI analysis, we did not find any significant difference in condition contrast of interest (stop correct-stop incorrect), p<0.05 corrected (See Figure 7).

Patients:

Similar results were observed for the patient population. When selecting the (R) IFG as the seed region on interest, we did not find any significant within group (patients) PPI analysis, we did not find any significant difference in the condition contrast of interest (stop correct-stop incorrect), $p<0.05$ corrected (See Figure 8).

Multiple Regression analysis--Behavior

The dependent variable (DV) of SSRT was computed for all subjects. A one-way ANOVA did not yield significant between group differences for SSRT $F(2)=0.022$, $p=0.88$, $\eta^2 = 0.03$. Therefore, SSRT was not entered into the regression analysis.

DISCUSSION

We examined the TBFC among regions involved in the SST in people with SZ or SA and healthy controls while the subjects performed the task in the MRI. Results indicated no significant between group differences on any of the ROI pairs. However, two region pairs showed a trend in significance, (R) preSMA-(R) GP and (R) STN-(L) GP, when not corrected for multiple comparisons. Post hoc analysis showed that this decrease was exclusively located in the inpatient population and may reflect additional impairment in their ability to recruit these regions during task performance. This set of non-significant connectivity results may be because a larger sample size of inpatients is needed to highlight these dysconnectivity patterns. If the task based connectivity among these region pairs had reached significance, they may have helped explain the observed differences in behavioral performance among the inpatient population. Recall,

that the behavioral deficits were exclusively concentrated within the inpatient population.

Although there are no direct connections between the preSMA and the GP, functional dysconnectivity among these regions might indicate impairment within the mechanism that underlies motor inhibitory control, the preSMA and its subsequent connections to the GP via the ST (and the resulting increase in premotor activation leading to an action). This type of dysconnectivity could have been used to make inferences about behavioral performances on stop accuracy performance on the task if the latter measure had not been dynamically altered.

Results indicate a trend in significance in the FC between (R) STN-(L) GP. If this trend had reached significance (perhaps with increased sample size) and if the stop task had not been dynamically manipulated to yield a p(inhibt|signal)=0.50, then the observed dysconnectivity might have helped explain the significant difference in stop accuracy among the inpatient population. Decreased connectivity between the STN and GP (presumably via the corpus callosum, in order to account for the observed interhemispheric dysconnectivity) results in the decreased inhibitory effects of GP on the thalamus and thus increased motor action.

However, as mentioned in the previous chapter, the use of a dynamically altered algorithm to determine stop accuracy precludes the use of this measure to make inferences about between group differences in stop accuracy. Specifically, according to the horse-race model, as the SSD increases, the p(inhibit|signal) decreases and subjects are more likely to incorrectly respond to

the stop stimuli. However, our results indicate otherwise. Both controls and patients showed an increase in stop accuracy above a SSD of 550 ms when compared to below an SSD of 550 ms, suggesting that both group performed better at longer SSDs. This improved performance is reflected in the % of SSD above 550 ms. In controls, 79%, SD=+/- 10.1 of all SSDs were above 550 ms whereas 67.47%, SD= +/- 25.9, of all SSD in patients were above 550 ms. Because the subjects are spending the majority of the time above an SSD of greater than 550 ms (As reflected by the % of SSD above 550 ms) and because their stop performance improves as SSD increases, the task may lack construct validity. This violation of the underlying assumption of the horse-race model makes the resulting stop accuracy measure and the subsequent group comparison invalid.

Additionally, both subject groups showed an increase in go reaction time as a function of SSD, suggesting that they took longer to respond to the go accuracy component of the SST. This increase in go reaction time suggests that the subjects employed a waiting strategy to see if the stop signal would appear before making or withholding a response. This increase in go reaction time might explain the observation of increased stop accuracy on the SST. Thus, the observed differences in stop accuracy may not reflect a true difference on the groups' ability to correctly withhold a response but rather may reflect their ability to adopt a strategy to perform on the task. Leotti and Wager (2010) have found that strategies such as waiting can influence SST performance.

For these reasons, the use of the adaptive algorithm to make inferences about population performance on the stop accuracy measure is not valid.

Importantly, the predominant neurotransmitter among the region pairs that show non-significant (but trending) decreases in dysconnectivity is glutamate. Glutamate is the most abundant excitatory neurotransmitter in the brain. The glutamate hypothesis of SZ, models the pathological mechanisms linked to its signaling and was based on genetic, clinical and neurological findings pointing to a hypofunction of the neurotransmitter. The decrease in connectivity observed among regions mediated by glutamate may provide further evidence for the glutamate hypofunction in SZ (Javitt and Zukin, 1991).

Our study also assessed how the dysconnectivity patterns that were observed during rest changed during task performance. Recall, that inpatients showed significant decreases in connectivity among four region pairs, the (L)Thal-(R)GP, (R)STN-(R)GP, (R)STN-(L)Thal, and the (L)ST-(R)GP whereas the outpatients only showed deficits among the two latter region pairs. Interestingly, patients showed a normalization of region pairs that exhibited dysconnectivity at rest, except with one region pair: (R)STN-(R)GP. Importantly, this region pair was exclusively impaired in the inpatient population and this significance might reflect a lack of *complete* normalization among the inpatient population.

We also assessed the correlation between TBFC and behavioral performance and observed that go accuracy among the inpatient population is negatively correlated to the FC among the (L)GP-(L)Thal, such that as the

connectivity among the region pair increases, go accuracy decreases. Although initially this observation may not be easily understood, further speculation suggests a possible explanation. Recall that an observation of impaired dysconnectivity does not necessarily imply a decrease in connectivity but rather an abnormal connectivity. Recall that as the connectivity between the GP and the Thal increases the normally inhibitory GABAergic projections from the GP to the Thal resulting in a net inhibition and thus decreased responses.

The difficulty of interpreting this result arises due to an inability to distinguish at rest those structures involved among the direct pathway (go pathway) and indirect pathway (stop pathway).Although our study looked at the change in connectivity between the (R)IFG-(R)preSMA during stop correct vs. stop incorrect trials, we did not distinguish the *pattern* of dysconnectivity during go trials only and stop trials only. Doing so might shed light on which region pairs are differentially disconnected as a function of trial type and future studies should aim to address this limitation.

In contrast to studies showing a group difference in SSRT among patients and controls, including our own (Nolan et al., 2011), the present data failed to replicate this finding. In our dataset, there were no significant differences among patients and controls on the SSRT, and this non-significant finding remained after splitting the patient group into inpatients and outpatients. Additionally, contrary to our hypothesis, we observed a between group difference in stop and go accuracy, with patients unable to perform the task.

There are several possible explanations for the observed lack of significant SSRT difference between controls and patients. The version of the SST we used had some design flaws that may have contributed to the observed lack of significant results. First, according to the horse-race model, as the SSD increases, the p(inhibit|signal) decreases and subjects are more likely to incorrectly respond to the stop stimuli. However, our results indicate otherwise. Both controls and patients showed an increase in stop accuracy above a SSD of 550 ms when compared to below an SSD of 550 ms, suggesting that both group performed better at longer SSDs. This improved performance is reflected in the % of SSD above 550 ms. In controls, 79%, SD=+/- 10.1 of all SSDs were above 550 ms whereas 67.47%, SD= +/- 25.9, of all SSD in patients were above 550 ms. Because the subjects are spending the majority of the time above an SSD of greater than 550 ms (As reflected by the % of SSD above 550 ms) and because their stop performance improves as SSD increases, the task may lack construct validity. This violation of the underlying assumption of the horse-race model makes the resulting stop accuracy measure and the subsequent group comparison invalid.

Additionally, both subject groups showed an increase in go reaction time as a function of SSD, suggesting that they took longer to respond to the go accuracy component of the SST. This increase in go reaction time suggests that the subjects employed a waiting strategy to see if the stop signal would appear before making or withholding a response. This increase in go reaction time might explain the observation of increased stop accuracy on the SST. Thus, the

observed differences in stop accuracy may not reflect a true difference on the groups' ability to correctly withhold a response but rather may reflect their ability to adopt a strategy to perform on the task (Leotti and Wager, 2010).

SST was conducted in the MRI and this method of testing may have contributed to the observed results. Since all subjects must perform at an accuracy level of 80% accuracy level on the SST before performing the task in the scanner, we should have expected to see similar results from the MRI session. However, as data presented earlier shows, neither controls not patients had a mean accuracy of greater than 72% on the go trials. This may suggest that people tend to perform worse inside the scanner than outside. In order to more accurately assess the efficacy of using one version of the task over the other, studies comparing both tasks outside of the scanner must be conducted.

In order to make inferences about the latency of the stopping process between groups, the groups should differ in only their SSRT and not on any other behavioral measure, such as stop and go accuracy. Between group behavioral difference in these measures introduces additional confounds, such as floor effect, that prevent one from being able to make inferences about response inhibition and the latency of the stopping process. As reported earlier, results from the SST show between group difference in both stop and go accuracy, suggesting that people with SZ may have impairment not in response inhibition but rather with adequately completing the task. Future studies should concentrate on designing or choosing a task (such as the STOP-IT task,

described in subsequent chapter) that better adheres to the principles outlined in Logan (1994).

Based on Duann et al., (2009), we hypothesized increased functional connectivity between the (R) IFG and the (R) preSMA during correct stop vs. incorrect stop trials. However, contrary to our hypothesis, did not show significant results for either controls or patients in the PPI analysis for the condition of interest, stop correct minus stop incorrect. There might be several reasons why we failed to see significant results in the PPI analysis.

First, PPI analysis does not work very successfully with fMRI data and is better suited for data gathered by PET because a significant effect with the interaction term requires a signal change of over 2% (Friston 1997), which is less likely with MRI.

Second, PPI analysis gives information about changes in functional connectivity as a function of change in the task condition. It doesn't give information about areas that maintain their connectivity as a function of time. Therefore, a lack of significant result doesn't imply a lack of connectivity. At most, it is an indication of a lack of change in connectivity. Future studies using PPI should, if possible, focus on PET studies.

A major limitation of the study is that all patients were receiving antipsychotic medications at the time of the scanning. A review by Davis et al., (2005) suggested that treatment with antipsychotic medications results in normalization of brain functions, so that it is more similar to the brain functions in controls. However, even if treatment with antipsychotics medications were shown

to normalize functional connectivity, the presence of observed differences in RSFC suggests that our results are likely attributable to the disease rather than pharmacological therapy. However, the confounding effects of medication on normalizing functional connectivity cannot be ruled out until future studies with first episode SZ and medication-naïve patients are conducted.

We investigated functional connectivity during task performance as well as functional connectivity as a function of task condition among regions involved in response inhibition in people with SZ or SA and controls. Although we did not find any significant results in either TBFC or PPI, results did indicate a trend in significance in TBFC among structures involved in response inhibition along with motor control. These results suggest the need for further studies to better elucidate the connection between decreased functional connectivity and task performance.

Figure 1A: Pictorial representation of the assumptions underlying the horse race model. It depicts how the probability of responding [p(respond)] and the probability of inhibiting [p(inhibit)] depend on the distribution of the go reaction times (indicated as the distribution of primary-task RT) and the stop signal delay (Figure from Logan & Cowan, 1984).

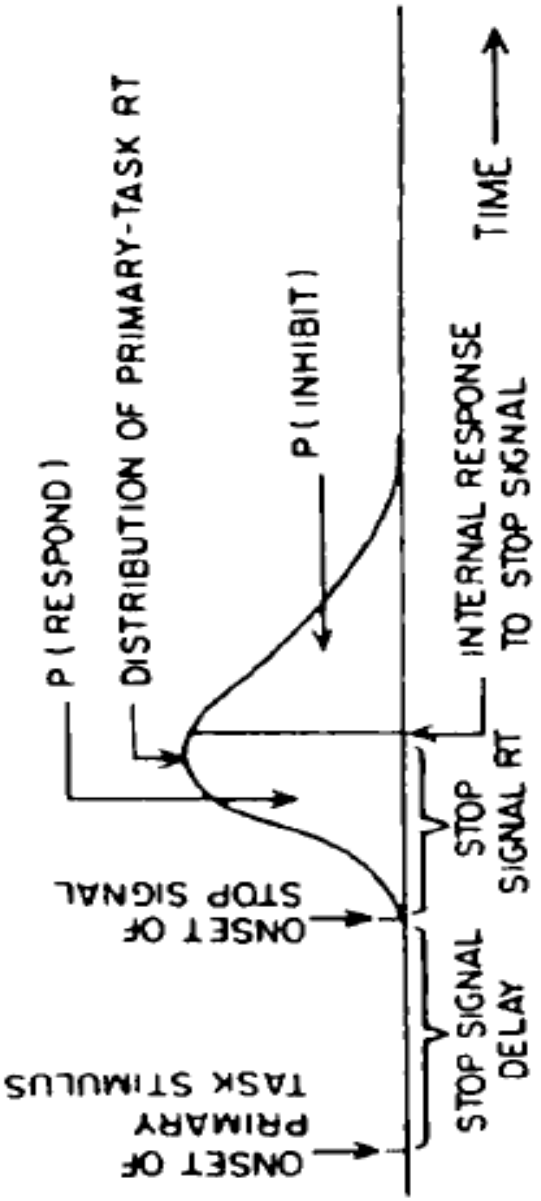


Figure 1B: Graphic representation of the predicted probabilities of responding [p(respond)] based on the independent horse-race model (left panel) and the corresponding inhibition function (right panel). (A, B and C) Graphic representation of p(respond) for every stop signal delay and the corresponding inhibition function as a result of shifting the go reaction time to the right (Figure from Verbruggen & Logan, 2009).

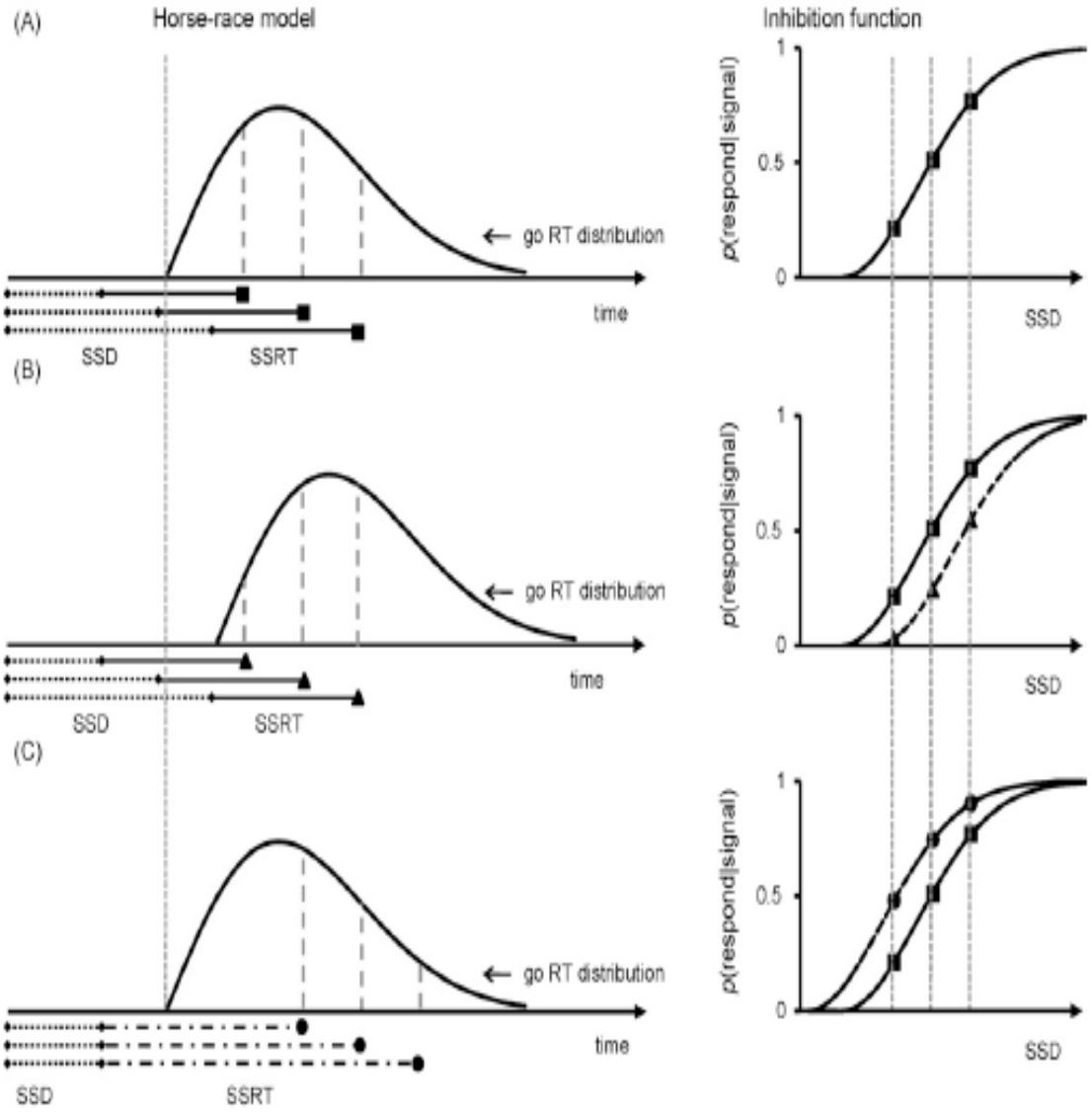


Figure 2: Stop Signal Task. “+” represents fixation point. “X” and “Y” represent the go trials where the subject is instructed to respond by pressing the right and left button, respectively. The red box represents the stop trial where the subject is instructed to withhold their response to X and O.

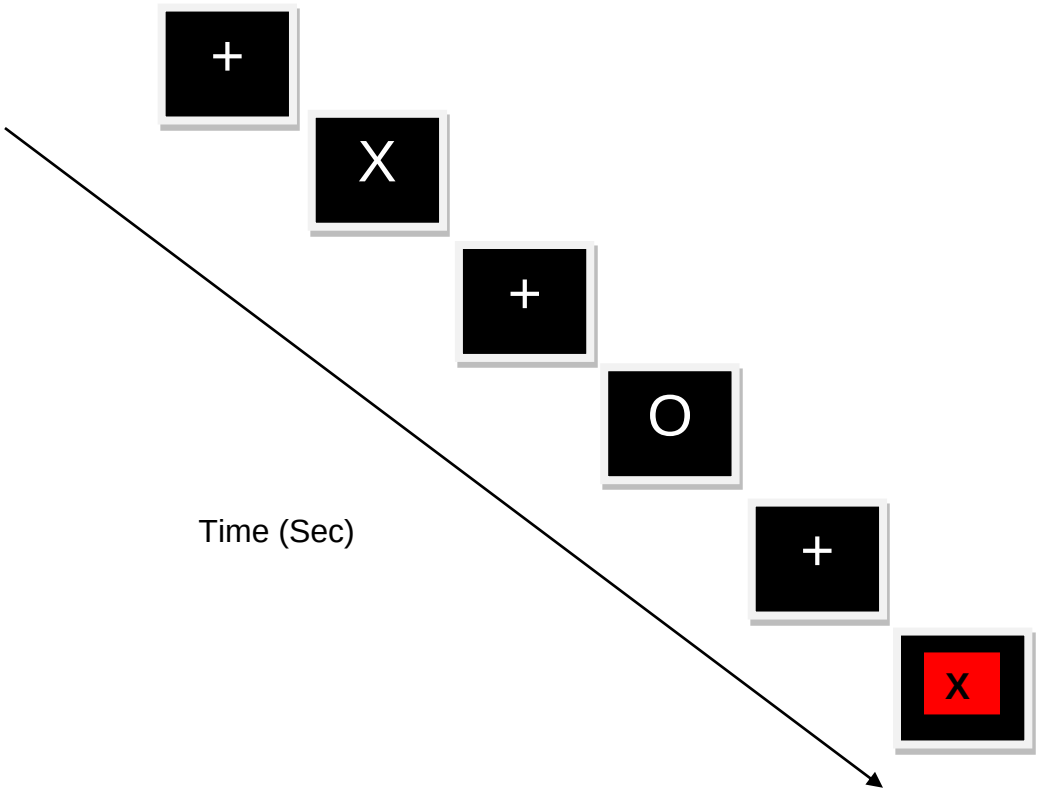
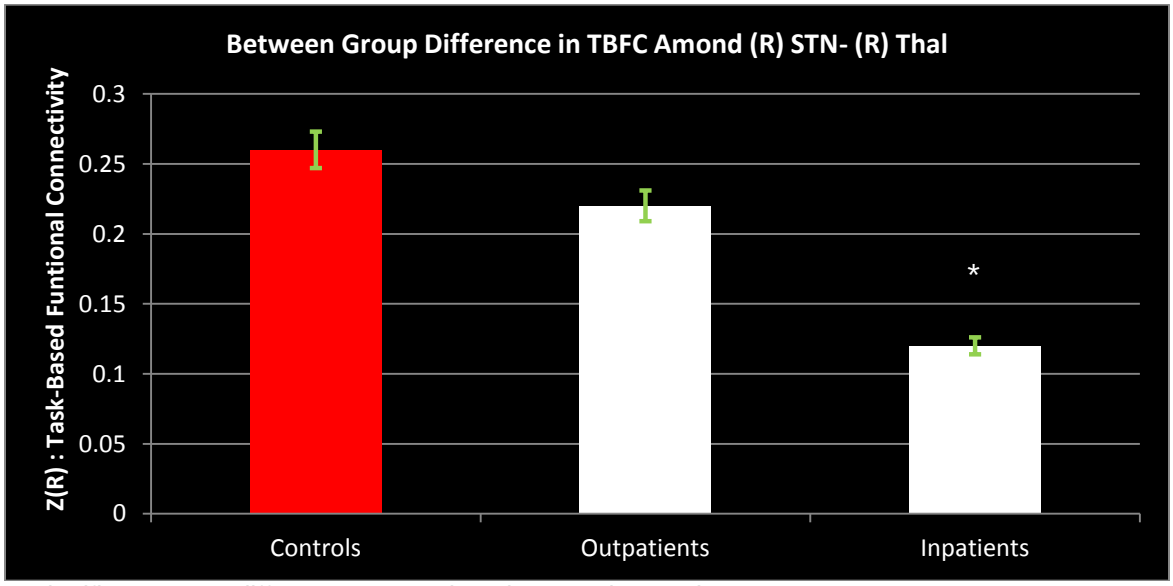
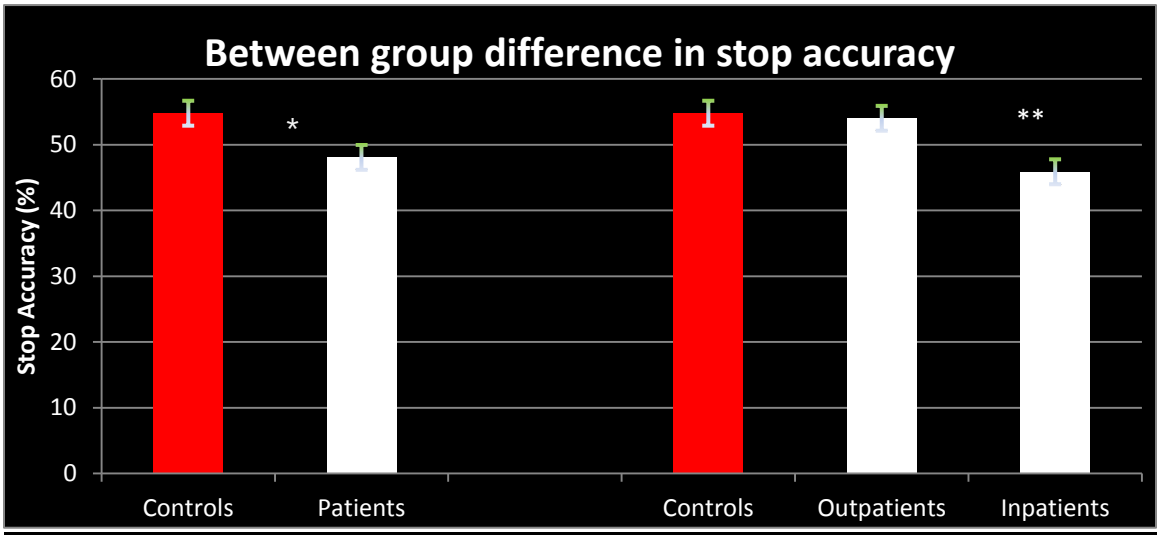


Figure 3: Between group difference among healthy controls, inpatients and outpatients in task-based functional connectivity.



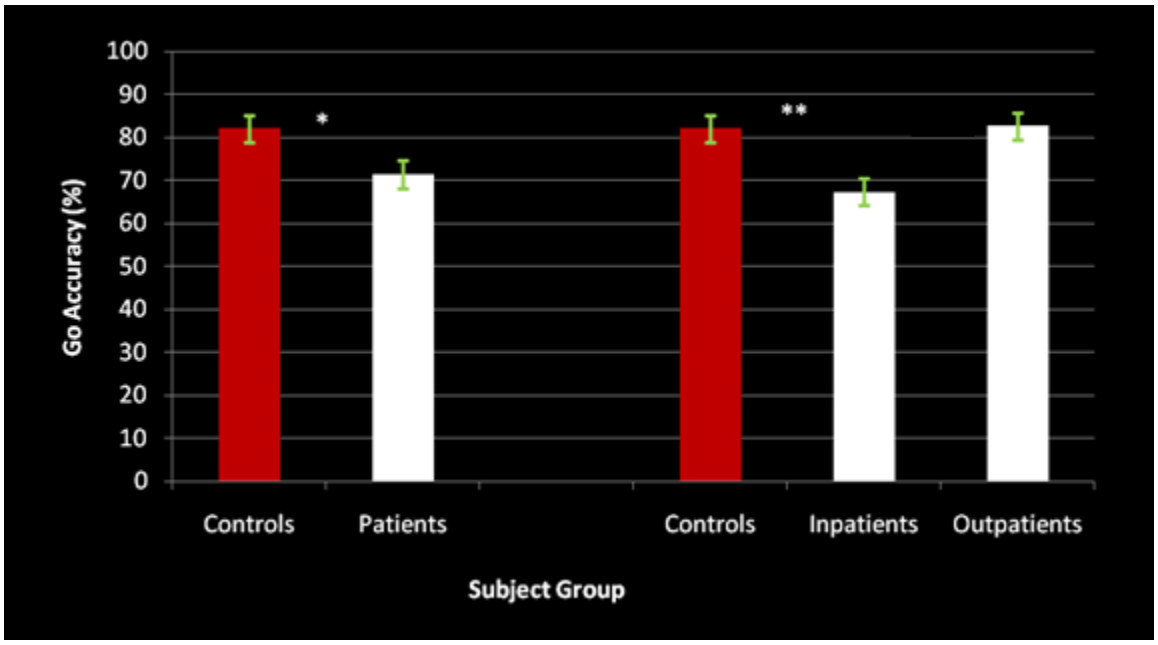
*= significant group difference among inpatients and controls, p=0.05

Figure 4A: Between group difference on stop accuracy (STOPACC)



*=significant between group difference, p=0.03
**=significant difference between controls and inpatients, p=0.032

Figure 4B: Between group difference on go accuracy (GoACC)



*=significant between group difference, p=0.005
**=significant difference between controls and inpatients, p=0.004

Figure 5: Correlation between go accuracy (%) and FC between (L)GP-(L)Thal among inpatients with SZ or SA

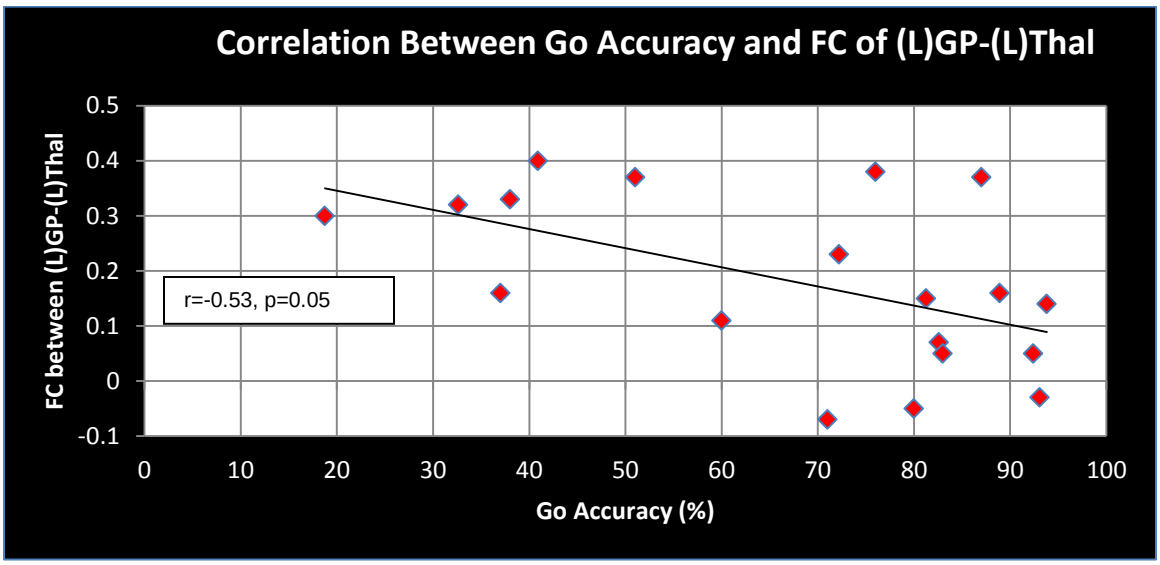


Figure 6: Stem and leaf diagram of stop accuracy in outpatients with SZ or SA

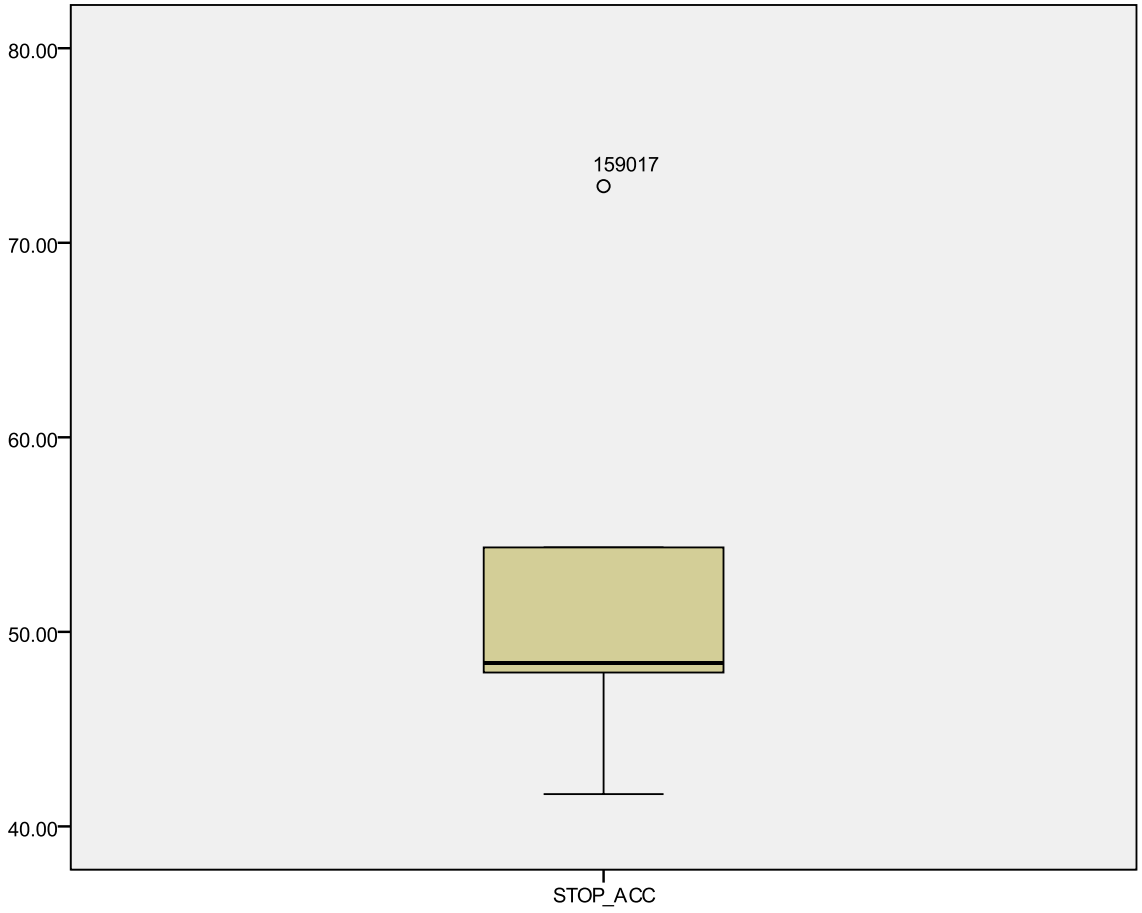


Table 1: Demographic profiles of patients with SZ or SA and healthy controls

Characteristics	Patients with SZ or SA (N=26)	Healthy Controls (N=26)	t/χ2 value	p-value
Age (years)	39.23	39.73	0.188	0.85
Sex(M/F)	21/5	19/7	0.74	0.43
Race(White/Black/Other)	8/14/4	10/11/5	0.70	0.76
Diagnosis(SZ/SA)	22/4	N/A	N/A	N/A
Inpatients/Outpatients	19/7	N/A	N/A	N/A

Table 2: Between group difference among controls and patients on RSFC and TBFC

RSFC	ROI Pairs	t-value	p-value
	(L) ST- (R) GP	4.46	0.0005
	(R) STN- (L) Thal	3.98	0.0005
	(R) STN-(R) GP	3.4	0.001
	(L) Thal- (R) GP	3.7	0.001
TBFC	(L) ST- (R) GP	0.77	0.44
	(R) STN- (L) Thal	1.4	0.17
	*(R) STN-(R) GP	2.4	0.02
	(L) Thal- (R) GP	1.8	0.07

*= significant between group difference, p=0.02

Table 3: Region pairs that exhibit a trend in TBFC. Between group difference among controls, inpatients and outpatients using one way ANOVA

ROI Pair	F-value	p-value	η^2
(R) STN- (R) Thal	3.02	0.06	0.13

Table 4: Mean TBFC among patient subpopulation and healthy controls among (R)STN-(R)Thal

Subject Group	Mean TBFC
Controls	0.26
Outpatients	0.22
Inpatients	0.12

Table 5: Behavioral data from the SST for controls and patients with SZ or SA

Subject Group	Mean Go Accuracy (%)	SD	SE	Mean Stop Accuracy (%)	SD	SE	Mean SSRT (ms)	SD	SE	Mean GoRT (ms)	SD	SE
Healthy Controls (N=26)	85.82	13.2	2.59	54.8	11.03	2.3	109.47	93.15	18.27	666.06	88.58	17.37
Patients with SZ or SA (N=26)	71.46	22.66	4.44	48.08	11.4	2.2	122.65	109.14	21.4	668.53	90.71	17.79

Table 6: Behavioral data from the SST for inpatients and outpatients with SZ or SA

Subject Group	Mean Go Accuracy (%)	SD	SE	Mean Stop Accuracy (%)	SD	SE	Mean SSRT (ms)	SD	SE	Mean GoRT (ms)	SD	SE
Inpatients (N=19)	67.34	23.75	5.45	45.89	11.03	2.53	124.82	113.67	26.08	681.24	64.3	14.75
Outpatients (N=7)	82.64	15.71	5.94	54.03	10.97	14.15	116.76	103.99	39.31	634.03	141.36	53.43

Table 7: Between group difference on behavioral measures on the SST among controls and patients with SZ or SA using one way ANOVA

Behavioral measure	F-value	p-value	η^2
Go accuracy	5.941	0.005	0.8
Go reaction time	0.72	0.492	0.97
Stop accuracy	3.66	0.03	0.86
SSRT	0.123	0.884	0.99

CHAPTER 4: ANCILLARY STUDIES 1.0 AND 2.0

STUDY 1.0: ASSESS BETWEEN GROUP DIFFERENCE AMONG RESPONSE INHIBITION USING THE STOP-IT TASK

STUDY 2.0: ASSESS RSFC AS A FUNCTION OF TASK AMONG PATIENTS AND CONTROLS

ANCILLARY STUDY 1.0: ASSESS BETWEEN GROUP DIFFERENCE AMONG RESPONSE INHIBITION USING THE STOP-IT TASK:

The STOP-IT task, designed by Verbruggen et al., (2008) and freely downloadable (http://www.psy.vanderbilt.edu/faculty/logan/#stopit) is similar to the SST we utilized. They are both based on Logan's (1984) horse-race model, allows for the calculation of an unobservable event, the stop signal reaction time, and the SSD is dynamically changed as a function of subject performance. However, there are important distinctions between the two versions of the stop task.: 1: the SST has a visual component as part of the inhibition as opposed to the STOP-IT which contains an auditory component and 2. The SST was performed in the scanner whereas the STOP-IT was conducted outside of the scanner. This difference in environment may have an impact on behavioral performance observed between the two tasks.

In the SST, the stop trial is a red box superimposed on the go cue (the "X" or "Y"). In the STOP-IT task, the stop trial is indicated by an auditory cue that follows the go trial (square or a circle). There is data suggesting that the auditory SSRT are longer than visual SSRT (Cabel et al., 2000).

The SSD used in the STOP-IT task dynamically changes from 250 ms to 600 ms, increasing or decreasing by 50 ms. This is in contrast to the SST study in which the SSD ranges from 250ms to 750ms. Logan (1994) suggests that the shortest delay should be close to zero whereas the longest should be no longer than the mean go reaction time, around 500 ms. Our version of the SST used a SST 250 ms greater than the recommended SSD. Additionally, it was also greater than the average go reaction time of the subjects, mean go reaction

time=667.30 ms, SD=88. However, this mean is an inaccurate reflection of the actual go reaction time because our results suggest that subjects may have waited to respond in trials with longer SSDs. In his seminal papers, Logan et al., (1984 and 1994) discuss the methodology of determining the stop signal delay. In it, they chose their SSD based on mean go reaction time to *only* go trials so as to get unbiased results—thus, the stop trials weren't included in this calculation. Unfortunately, we did not define our SSD using this method and the mean go reaction we used was filtered out of a dataset that included both go and stop trials.

Based on the specific STOP-IT parameters (such as the use of a less complex visual cue), and the decrease in the emphasis of the stop trial, we hypothesized that on the STOP-IT task, people with SZ would exhibit no significant between group difference on either stop or go accuracy. Additionally, we hypothesized that people with SZ would show increased SSRT when compared to healthy controls.

METHODS

Subjects

Six patients with DSM-IV diagnosis of SZ (N=4) or SA (N=2) and seven controls participated in the pilot study. Of the four SZ patients, 3 were diagnosed as undifferentiated subtype and 1 as paranoid subtype (see Table 1). The study was approved by the NKI Institutional Review Board. All subjects provided voluntary informed consent and were compensated $10/hour for their participation. At the time of the study, all patients were on antipsychotic medications.

The Structured Clinical Interview for DSM-IV-TR Axis I Disorders -- Patient edition (SCID-I/P) was administered to patients and the SCID -- Nonpatient version (SCID-I/NP) was administered to controls by trained raters. Subjects with a DSM-IV Axis I diagnosis other than SZ or SA disorder, including psychotic mood disorder, alcoholism or substance dependence within the past 6 months were excluded from the study, as were subjects with any clinical neurological conditions. Controls as well as outpatients living on the grounds of the Rockland Psychiatric Center (RPC) were recruited from NKI's Volunteer Recruitment Program (VRP). Inpatients were recruited from the two 12-bed research units located at NKI. These units comprise the Clinical Research and Evaluation Facility (CREF) and primarily receive its patients from RPC. We confirmed the absence of drugs of abuse in outpatients and controls by performing urine toxicology screens.

Procedure

All subjects participated in both the STOP-IT task as well as the SST. The SST was presented within the MRI and the STOP-IT was performed outside the scanner.

The STOP-IT task

All subjects participated in 4 blocks of the STOP-IT task. Subjects are presented with a primary task, differentiating circle and square. On no-signal trials, which account for 75% of trials, subjects are instructed to respond to the stimulus as fast and accurately as possible. On stop-signal trials, which account for 25% of trials, the primary task is followed by an auditory stop signal (750Hz, presented

for 75 ms, and subjects are instructed to withhold their response (See Figure 1). The data are collected and saved as a tab-delimited text file.

The Stop Signal Task (SST)

In this task, participants are presented with either a letter “X” or a letter “O.” They are told to press the right button when the letter “X” is presented and the left button when the letter “O” is presented. These represent the Go stimuli since the subjects are not told to inhibit their responses. In the Stop stimuli condition (25% of trials), the letter “X” or “O” is followed by a red square (See Figure 2 in Chapter 3).

The time between the presentation of the “X” stimulus and the “O” stimulus, the SSD, was dynamically changed from 250 ms to 750 ms in accordance with the subject’s performance, such that when the subject correctly withholds a response during the stop trial, the SSD increased by 50 ms, up to a maximum SSD value of 750msec. Alternatively, if the subject responded incorrectly to a stop trial, then the SSD decreased by 50msec, down to a minimum SSD value of 250msec.

Behavioral Analysis

The STOP-IT task is accompanied by a program known as ANALYZE-IT. ANALYZE-IT calculates, for each subject, mean SSD, SSRT, go reaction time, go accuracy and stop accuracy. The first block of each subject is not entered in the analysis.

Data from the SST were used to calculate go accuracy, stop accuracy (StopACC) as well as the stop signal reaction time (SSRT) (please refer to Chapter 4 for a detailed explanation of the calculations).

RESULTS

Within this sample, SST results indicate no significant between group difference among controls and patients on any of the behavioral data : SSRT (controls: *M*=94.81 ms, *SD*=+/-111.96; patients: *M*=160.1 ms, *SD*=+/-112.46, p=0.32, Go accuracy (controls: *M*=71.43%, *SD*=+/-18.63, patients: *M*=70.31 %, *SD*=+/-18.6, p=0.94), GoRT (controls: *M*=663.49ms, *SD*=+/-57.57, patients: *M*=658.1 ms, *SD*=48.19, p=0.64) and StopACC (controls: *M*=44.8%, *SD*=15.32, patients: *M*=41.0 %, *SD*=12.87, p=0.86). See Tables 2 and 3. See Figures 2 and 3.

As hypothesized, results from the STOP-IT task showed no significant between group difference among controls and patients on most of the behavioral measures: Go accuracy (controls: *M*=92.33 %, *SD*=+/- 8.18, patients: *M*=89.07 %, *SD*=+/- 12.31), GoRT (controls: *M*=622.81 ms, *SD*=+/- 166.33, patients: *M*=732.35 ms, *SD*=73.64) and StopACC (controls: *M*=82.5 %, *SD*=+/-4.6, patients: *M*=76.59 %, *SD*=10.67). Additionally, as hypothesized, there was a between group difference on SSRT (controls: *M*=221.49 ms, *SD*=+/-53.24, patients: *M*=381.4 ms, *SD*=+/- 125.7) (see tables 4 and 5; see figures 4 and 5).

Additionally, we assessed the correlation between the SST and STOP-IT task on the response inhibition measure, SSRT. Controls exhibited a large correlation between the SST SSRT and STOP-IT SSRT, r=0.96, p=0.001. However, among the patient population, there was no significant correlation between the SST SSRT and STOP-IT SSRT, r=0.28, p=0.60. We also compared between-group difference in performance on the SST and the STOP-IT! task (see Figures 6- 8).

DISCUSSION

Interestingly, subject data from both the SST and the STOP-IT task revealed differential patterns of behavioral results. The SST was not sensitive enough to distinguish between group differences in any of the behavioral measures and thus this dataset could not be used to make inferences about differences in response inhibition among the subject populations.

The STOP-IT task, on the other hand, was able to distinguish between group differences on the behavioral measure of interest, the SSRT. Most importantly, the subjects did not differ significantly in their performance on any of the other behavioral measure (See Figures 7 and 8). The SSRT results from the STOP-IT data suggest that patients with SZ have increased stop latency (thus, the amount of time it takes to stop an already initiated response is increased). Controls, on the other hand, showed a decreased SSRT suggesting that they are better able to stop an already initiated response. A longer SSRT indicates poor response inhibition, and many studies have used prolonged SSRT as an index of impaired motor inhibitory control in patients with neurological or psychiatric conditions (Kooijmans et al., 2000; Rieger et al., 2003; Gauggel et al., 2004; Bekker et al., 2005; Bellgrove et al., 2006; Li et al., 2006b; Alderson et al., 2007; Sagaspe et al., 2007; Huddy et al., 2009; Huizenga et al., 2009; McAlonan et al., 2009). Thus, the observation of a significantly increased SSRT in the patient population may be indicative of impaired response inhibition.

The version of the SST we used had some design flaws that may have contributed to the observed lack of significant results.

According to the horse-race model, as the SSD increases, the p(inhibit|signal) decreases and subjects are more likely to incorrectly respond to the stop stimuli. However, our results indicate otherwise. Both controls and patients showed an increase in stop accuracy above a SSD of 550 ms when compared to below an SSD of 550 ms, suggesting that both group performed better at longer SSDs. This improved performance is reflected in the % of SSD above 550 ms. In controls, 79%, SD=+/- 10.1 of all SSDs were above 550 ms whereas 67.47%, SD= +/- 25.9, of all SSD in patients were above 550 ms. Because the subjects are spending the majority of the time above an SSD of greater than 550 ms (As reflected by the % of SSD above 550 ms) and because their stop performance improves as SSD increases, the task may lack construct validity.

Additionally, both subject groups showed an increase in go reaction time as a function of SSD, suggesting that they took longer to respond to the go accuracy component of the SST. This increase in go reaction time suggests that the subjects employed a waiting strategy to see if the stop signal would appear before making or withholding a response. This increase in go reaction time might explain the observation of increased stop accuracy on the SST. Thus, the observed differences in stop accuracy may not reflect a true difference on the groups' ability to correctly withhold a response but rather may reflect their ability to adopt a strategy to perform on the task (Leotti and Wager, 2010).See Tables 2 and 4.

In order to make inferences about the between group difference in response inhibition, the subjects must be able to perform the primary task, as reflected in the STOP-IT data results. Recall that the primary task of the SST requires the subject to distinguish between the letters “X” and “O” whereas the primary task of the STOP-IT requires the subject to distinguish between shapes: square and circle. Although results from both SST and STOP-IT indicate no between group difference on go accuracy (primary task), the subjects did not perform adequately on the SST’s primary task and suggests that both groups had difficultly performing the SST. Both controls and patients performed poorly on all aspects of the SST which may indicate a floor effect for the task. In sharp contrast to the data obtained from the SST, the data from the STOP-IT task shows that not only were both controls and patients able to perform the primary task but the only significant between group differences observed was for the SSRT, the measure of interest.

Third, studies show that as the complexity of visual stimuli increases, the ability to perform adequately on the task decreases. In the version of the SST that we used, the visual stop signal was complex—a red square. Contributing to this complexity is the finding that a red stimuli affects the magnocellular pathway of the visual system (Bedwell et al., 2003) which may impact higher level visual processing in people with SZ (Butler et al., 2001), such as the ability to adequately respond to the stop signal. In the STOP-IT! task however, the visual cues of the primary task were not complex—square or circle and the stop signal was an auditory cue. Although patients with SZ exhibit deficits in mismatch

negativity (MMN), which may affect higher level processing such as tone matching, the auditory stop signal utilized does not require the subject to differentiate the tones. Rather, the subjects simply need to recall that the tone represents a stop signal. One of the major limitations of this study is the small sample size. However, preliminary results suggest the STOP-IT task may be better suited to study response inhibition than the version of the SST that we used. Future studies using a larger sample size should be conducted to determine if the observed results hold.

Finally, the SST was conducted in the MRI whereas the STOP-IT was conducted on a lap top outside the scanner. This difference in testing methods may have affected the observed results. Since all subjects must perform at an accuracy level of 80% accuracy level on the SST before performing the task in the scanner, we should have expected to see similar results from the MRI session. However, as data presented earlier shows, neither controls not patients had a mean accuracy of greater than 72% on the go trials. This may suggest that people tend to perform worse inside the scanner than outside. In order to more accurately assess the efficacy of using one version of the task over the other, studies comparing both tasks outside of the scanner must be conducted.

In summary, the present finding demonstrates increased SSRT in people with SZ when administered the STOP-IT task vs. the SST. This increased SSRT may contribute to the observed deficits in response inhibition and may relate to the observed inability to regulate and control behavior (Teplin et al., 2005, Walsh et al., 2002). Additionally, our present finding suggests that the STOP-IT task

may be uniquely designed to study response inhibition in people with SZ and healthy controls when compared with the SST.

ANCILLARY STUDY #2: ASSESSING THE RSFC AMONG STRUCTURES INVOLVED IN RESPONSE INHIBITION AS A FUNCTION OF TASK.

In healthy controls, resting state functional connectivity is fairly constant across time (Fox and Raichle, 2007). However, many studies have shown that RSFC in pathologic populations are not quite so stable. For example: James et al., (2009) showed that stroke survivors showed normalization of their resting state functional connectivity in the motor network following rehabilitation of the upper extremity. Specifically, those stroke survivors that exhibited the greatest normalization of their RSFC also exhibited the greatest behavioral improvement. Many studies showed similar normalizations in RSFC (Park et al., 2011, McCabe et al., 2011; Goveas et al., 2011).

Based on these studies, we wanted to do an exploratory study to assess whether there would be changes in RSFC as a function of time. Due to the increased difficulty of follow up associated with a multi-day study, we decided to conduct a post task assessment of RSFC immediately after the subject performed the task. In accordance with previous studies, we hypothesized that the RSFC in healthy controls would remain stable across time. However, we didn't have an *a priori* hypothesis regarding the recovery of RSFC among patients with SZ.

METHODS

Subjects

Three people with DSM-IV-TR diagnosis of SZ (N=3 males) and eight non-psychiatric (N=5 males; N=3 females) age-matched subjects participated in the study. Of the three people with SZ, all were classified as outpatients (Table 1).

Additionally, of the patients diagnosed with SZ, two were subcategorized as undifferentiated and one as a residual.At the time of the study, all patients were receiving atypical antipsychotic medications only. The study was approved by the NKI Institutional Review Board. All subjects provided voluntary informed consent and were compensated $10/hour for their participation.

The Structured Clinical Interview for DSM-IV-TR Axis I Disorders Patient edition (SCID-I/P) was administered to patients and the SCID Nonpatient version (SCID-I/NP) was administered to controls by trained raters. Subjects with a DSM-IV Axis I diagnosis other than SZ or SA disorder, including psychotic mood disorder, alcoholism or substance dependence within the past 6 months were excluded from the study, as were subjects with any clinical neurological conditions. Controls as well as outpatients living on the grounds of the Rockland Psychiatric Center (RPC) were recruited from NKI's Volunteer Recruitment Program (VRP). We confirmed the absence of drugs of abuse in outpatients and controls by performing urine toxicology screens. All subjects were negative in their toxicology screen.

Procedure

<u>MRI Image Acquisition</u>

The study was performed on a 3.0 Tesla Siemens Tim Trio system (Erlangen, Germany) housed in the Center for Advanced Brain Imaging at NKI. Head stabilization was achieved using cushions and all subjects wore ear plugs to attenuate noise.

Because of possible effects of sedatives on functional connectivity (Kerssens et al., 2008), patients were not tested on any measure within 8 hours of the administration of a PRN medication. All subjects underwent an MRI scan where manual shimming procedures were performed and scout images were acquired. A six minute resting state MRI scan was also acquired before the subject completed the in-scanner task. This condition is referred to as pre-task condition. Before the six minute resting state scan, all subjects were instructed to lie still with their eyes closed and stay awake. Once the subject completed the MRI task, a second six minute resting state MRI was also acquired. The parameters and the directions given to the subject remained the same. This condition is referred to as the post-task condition.

Image sequence acquisition:

Subjects were scanned using a six minute echo planar imaging (EPI) sequence (TR = 2sec, TE = 30ms, FOV = 240mm, matrix = 96^2, 34 2.8 mm slices, IPAT = 2). The first five volumes are discarded to allow for T1-relaxation. A magnetization prepared acquisition of a gradient echo (MPRAGE; TR = 2500 ms, TE = 3.5 ms, flip angle = 8 deg, effective TI = 1200 ms, 256 x 256 matrix, FOV = 256 mm, NEX = 1, 192 slices, 1 mm slice thickness, 0 mm skip) was acquired for image registration and segmentation.

Image pre-processing

BOLD images were converted into NIFTI format. Resting state data were preprocessed using scripts from the 1000 Functional Connectomes project (http://www.nitrc.org/projects/fcon_1000/; Biswal et al., 2010). These scripts motion corrected the data, smoothed using a Gaussian kernel of 5 mm full-width at half-maximum (FWHM), band-passed, scaled, and detrended the 4D time series.

The FCONN scripts were also used to skullstrip and segment the MPRAGE using FMRIB Software Library's (FSL's) FMRIB's automated segmentation tool (FAST) program. Segmented images along with the ROI images were transformed to 2x2x2 mm^3Montreal Neurological Institute (MNI) space using FSL's FMRIB's Linear Registration Tool (FLIRT) program. The WM and CSF images, as well as the global image were used as masks to extract time series for each of these compartments along with the motion parameters obtained from Analysis of Functional NeuroImage (AFNI) to remove spurious sources of variance. The preprocessed 4D time series were then residualized for these covariates of no interest using FSL's fMRI Expert Analysis Tool (FEAT) program. Time series data for each ROI were extracted from these residualized data and retained for correlation analysis. Temporal filtering between 0.01Hz and 0.1Hz was also done.

RSFC analysis

To determine the RSFC between our ROIs, we assessed BOLD signal in rIFG, STN, GP, ST, preSMA and the Thal. We followed Aron and Poldrack (2006) and

placed an STN seed at [10, -15, -5] and preSMA seed at [6, 20, 50]. The seeds for GP, Thal and rIFG were placed according to the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). The time series he other ROIs after the pre-processed 4D (e.g., rGP with rIFG). We converted these correlations to Z-scores using Fisher's *r*-to-z transformation (Vincent et al., 2006). Correlations were performed on the (demeaned) time series data to provide FC between seeds.

RESULTS

Interregional correlations

For each subject, we computed twenty nine pairwise correlations among the predetermined ROIs. We then tested for group differences between patients and controls using independent sample t-tests. The alpha level was Bonferroni corrected for alpha inflation by setting p=0.05/29 (=0.002).

In the pre-task condition, no region pairs showed a significant between group difference in RSFC. However, one region pair showed a trend in significance,(with controls exhibiting significantly higher connectivity than patients: (R)STN-(R) GP (t(9)= 4.46, p=0.007(controls: *M*=0.30, *SD*=+/- 0.04;patients: *M*=0.08, *SD*=+/- 0.06(See Table 7).These results indicate that at least some of the structures involved in response inhibition exhibit aberrant resting state connectivity.

In addition, for each subject, the RSFC analysis was conducted on scans acquired during the second resting state condition. Recall that this second resting state scan was conducted immediately after the subject completed the in scanner

task. Again, we computed twenty nine pairwise correlations among the predetermined ROIs. We then tested for group differences between patients and controls using independent sample t-test. The alpha level was Bonferroni corrected for alpha inflation by setting the p-value to p=0.002 (See Table 8).

No region pairs showed a significant between group difference in RSFC among regions implicated in response inhibition. Additionally, no region pairs showed a trend in difference in RSFC. Interestingly, the decreased RSFC among patients observed during the pre-task condition was no longer present during the post-task condition (R)STN-(R) GP (t(9)=0.17, p=0.87 (controls: *M=0.28*, *SD*=+/- 0.14, patients: *M*=0.30, *SD*=+/- 0.12) (See Figure 9).

We conducted a paired sample t-test for both controls and patients to determine whether pre-task (R)STN-(R) GP and post-task (R)STN-(R) GP differed significantly between groups. As hypothesized, RSFC remained stable across time in healthy controls, t(7)=0.17, p=0.87. However, among people with SZ, RSFC seemed to normalize across time, t(2)=12.132, p=0.007 (See Table 9).

DISCUSSION

As hypothesized and in further support of previous studies, healthy controls exhibit stable RSFC across time. However, patients with SZ showed a normalization of the RSFC between(R) STN-(R) GP as a function of task performance. In line with previous studies that have correlated normalized RSFC with improved task performance, our finding may suggest that resting state

normalization may be related to improved behavioral performance. However, our study had multiple limitations that prevent us from making similar conclusions.

A major limitation of the study is the very small sample size in both the patient (N=3) and the control population (N=8). As a small sample size increases the chance that significant differences are false positive, our significant result may not necessarily point to an actual difference between the group.

Secondly, patient population that participated in this study were all living in an outpatient assisted living facility. Studies have shown a marked difference in social and cognitive functioning as well as severity of symptoms among inpatients and those treated in outpatient clinics (Knobler et al., 1999; Perlick et al., 1992). The data presented earlier (chapters 2 and chapter 3) show that inpatients have additional aberrant functional connectivity when compared to outpatients. Thus, the post-task normalization of RSFC observed in the patient population might be related to the relatively higher functioning and decreased severity of symptoms of the outpatient population. However, because our patient population did not include inpatients, we were unable to assess whether the post-task normalization was related to illness duration, social functioning or some other factor.

Furthermore, at the time of the study all three patients were receiving antipsychotic medications. A review by Davis et al. (2005) suggested that treatment with antipsychotic medications results in normalization of brain functions, so that it is more similar to the brain functions in controls. However, even if treatment with antipsychotics medications were shown to normalize

functional connectivity, the presence of observed differences in pre-task RSFC and the subsequent normalization of RSFC observed post-task suggests that our results are not likely only attributable to the pharmacological therapy. However, the confounding effects of medication on normalizing functional connectivity cannot be ruled out until future studies with first episode SZ and medication-naïve patients are conducted.

Future studies should focus on enrolling patients from both inpatient and outpatient facilities to ensure a more heterogeneous sample that better reflects the population. Additionally, information about duration of medication should also be collected so that its possible effects can be controlled for in the analysis. Also, although our study shows a post-task normalization of the RSFC, we are unable to correlate this normalization with behavioral performance. Therefore, future studies should include a second task session immediately following the post-task resting state. Further, we did not assess how long this normalization lasted. To test the lasting effects of this normalization, future studies might want to assess RSFC at predetermined time periods such as: immediately after task performance (as this study assessed), 1 month, 3 month and 6 months as seen in Park et al. (2011).

In summary, the present finding demonstrates that the outpatient population that participated in the study demonstrated a post-task normalization of their resting state functional connectivity among regions that showed a decreased in pre-task connectivity. This normalization may contribute to

improved task performance and future studies should attempt to test this relationship.

Figure 1: Graphical representation of the STOP-IT task. “FIX” represents the fixation point. The square and circle represent the primary task stimuli. The auditory tone, following the primary task represents the stop trial. SSD=stop signal delay; SDT= duration of stop signal; MAXRT=maximum reaction time (Figure from Verbruggen et al., 2009).

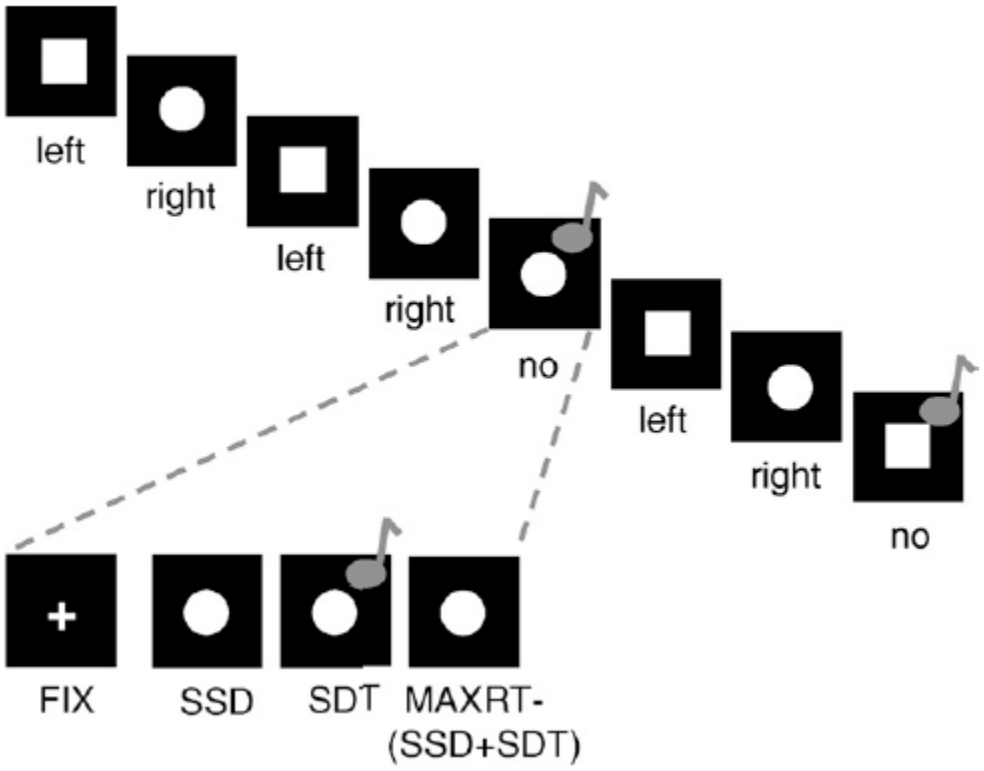
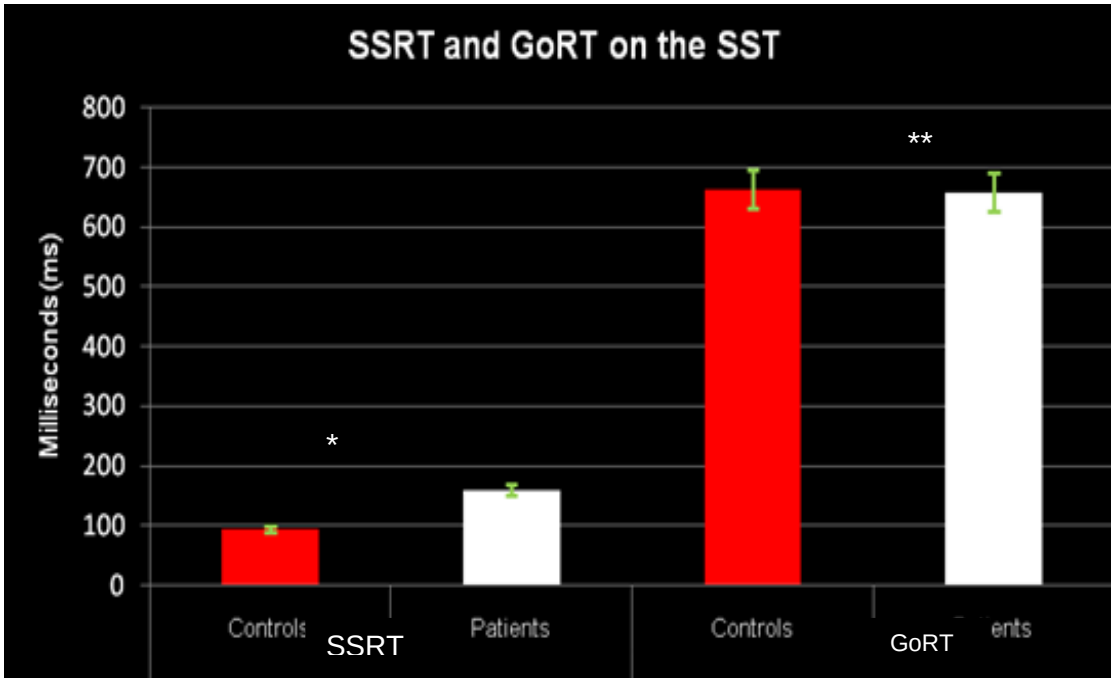


Figure 2: SSRT and GoRT results among healthy controls and patients with SZ or SA on the SST



*= no significant between group difference on SSRT, p=0.32
**=no significant between group difference on GoRT, p=0.64

Figure 3: Go and stop accuracy results among healthy controls and patients with SZ or SA on the SST.

Figure 4: Go and stop accuracy results among healthy controls and patients with SZ or SA on the STOP-IT task

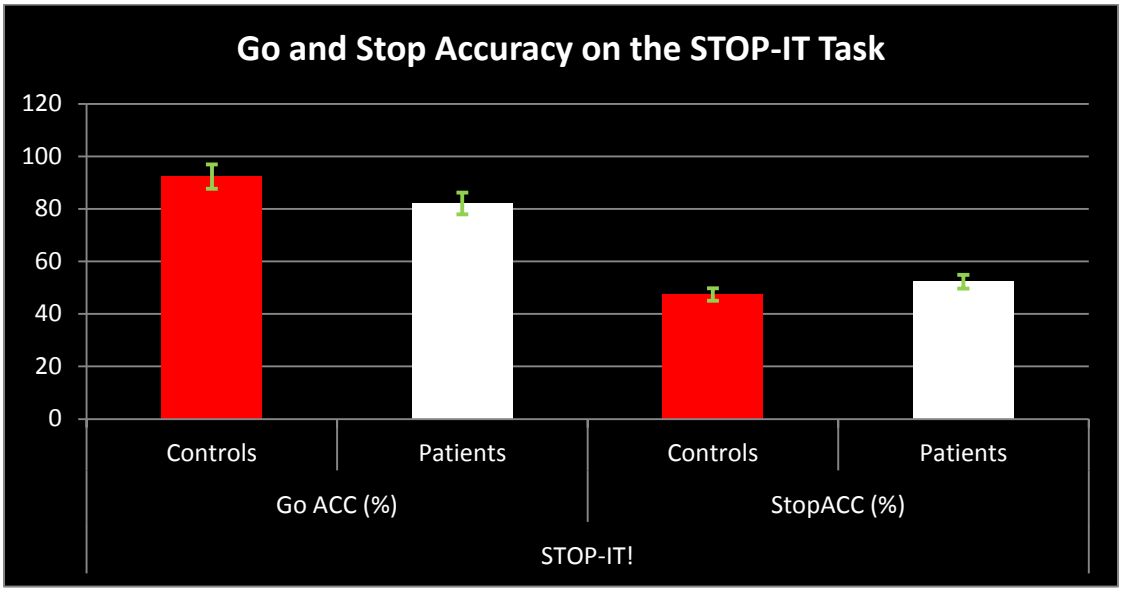

Go and Stop Accuracy on the STOP-IT Task
120
100
80
60
40
20
0
Controls
Patients
Controls
Patients
Go ACC (%)
StopACC (%)
STOP-IT!

Figure 5: SSRT and Go reaction time (GoRT) results among healthy controls and patients with SZ or SA.

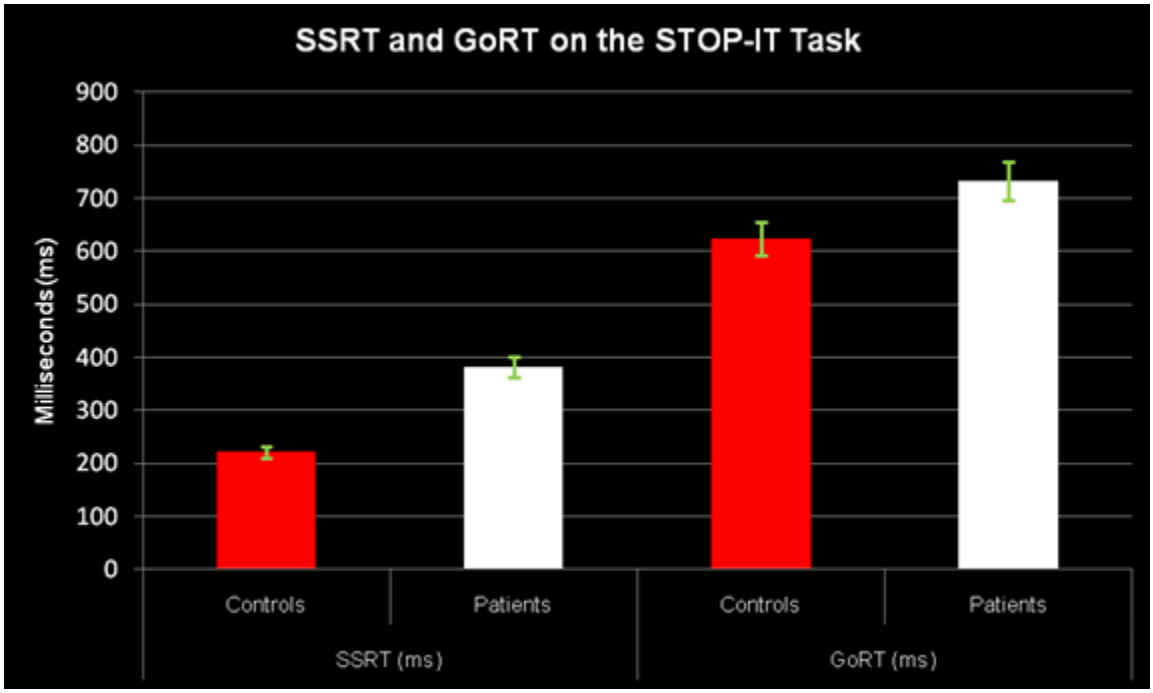
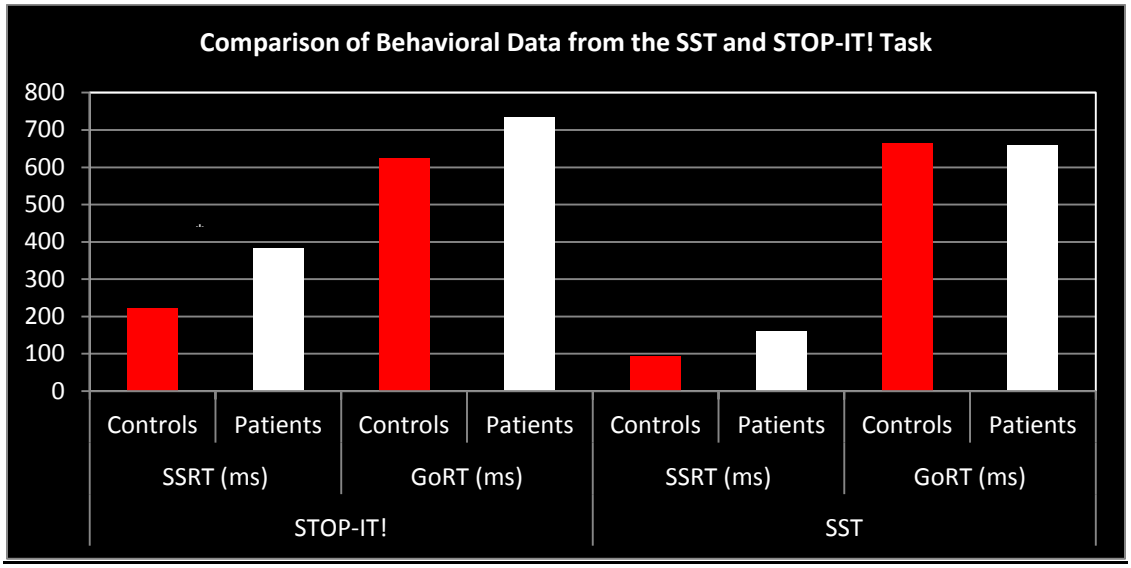


Figure 6: Correlation between STOP-IT and SST SSRT among healthy controls and patients with SZ or SA

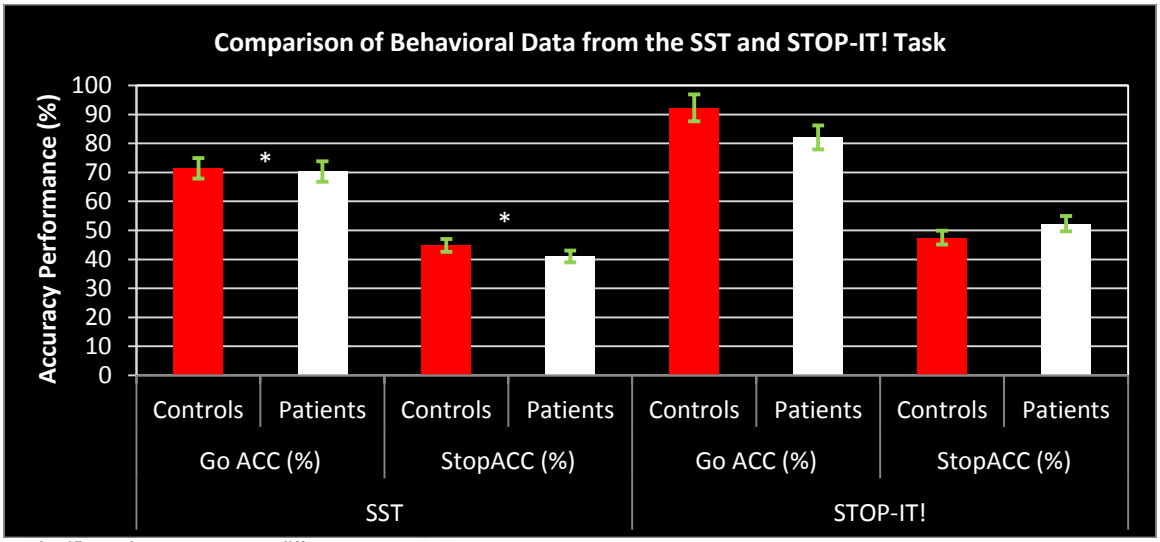
**=Correlation significant, p=0.001

Figure 7: Comparison of behavioral data from the SST and STOP-IT task for healthy controls and people with SZ or SA



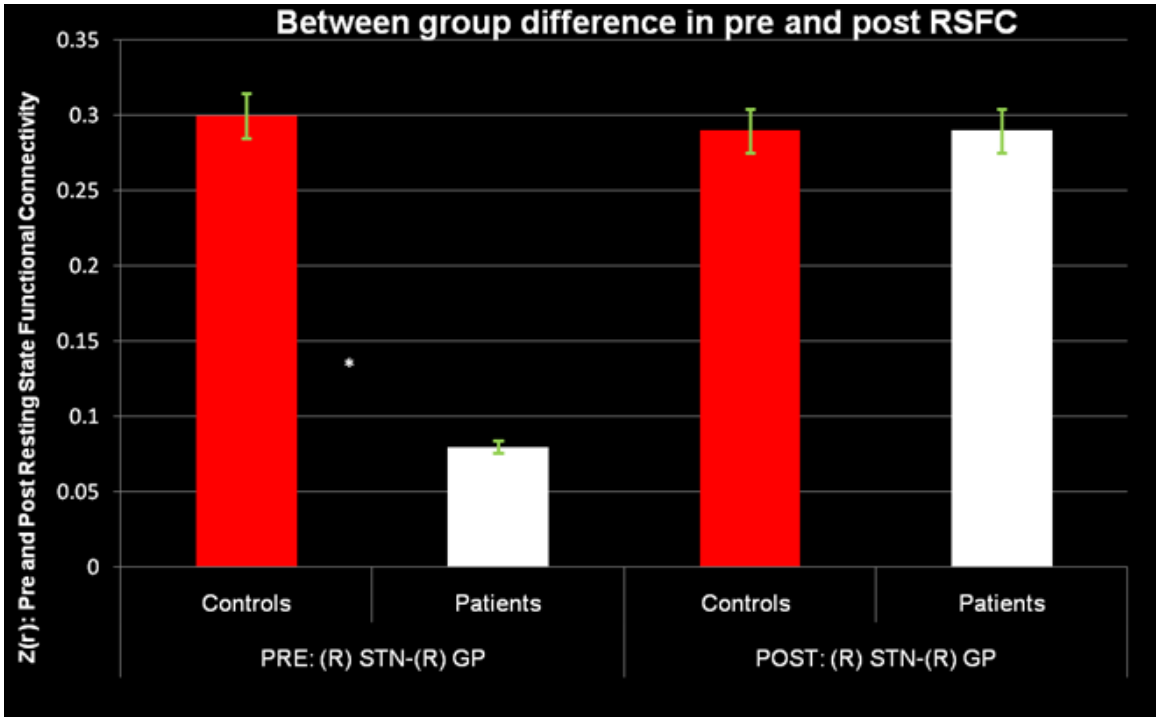
*=Only significant difference between controls and patients. Significant at p=0.001.

Figure 8: Comparison of behavioral data from the SST and STOP-IT task for healthy controls and people with SZ or SA



*=Significant between group difference, p = 0.005
**= Significant between group difference, p = 0.03

Figure 9: Pre and post task RSFC among (R) STN-(R) GP in patients with SZ or SA and controls



*= Correlation significant, p=0.007

Table 1: Demographic profiles of healthy controls and patients with SZ or SA.

Characteristics	Patients with SZ or SA (N=6)	Healthy Controls (N=7)	t/χ2	P
Age (years)	43.0	32.85	2.44	0.03*
Sex(M/F)	4/2	7/0	2.76	0.19
Race(White/Black/Other)	2/3/1	0/4/3	3.08	0.37
Diagnosis(SZ/SA)	4/2	N/A	N/A	N/A
Inpatients/Outpatients	5/1	N/A	N/A	N/A

*=Note: Significant between group difference in age.

Table 2: Behavioral Profiles on the SST task for Healthy Controls and Patients with SZ or SA

Subject Group	Mean Go Accuracy (%)	SD	SE	Mean Stop Accuracy (%)	SD	SE	Mean SSRT (ms)	SD	SE	Mean GoRT	SD	SE
Healthy Controls (N=7)	71.43	18.63	7.6	44.8	15.32	5.79	94.81	111.96	42.32	663.49	57.57	21.76
Patients with SZ or SA (N=6)	70.31	18.6	7.6	41	12.87	5.26	160.1	112.46	45.91	658.1	48.19	19.67

Table 3: Between group difference among healthy controls and patients with SZ or SA on the SST

Measure	df	t-value	p-value
Go Accuracy	11	0.082	0.94
Stop Accuracy	11	0.181	0.86
SSRT	11	1.05	0.32
GoRT	11	0.48	0.64

Table 4: Behavioral Profiles on the STOP-IT task for Healthy Controls and Patients with SZ or SA

Subject Group	Mean Go Accuracy (%)	SD	SE	Mean Stop Accuracy (%)	SD	SE	Mean SSRT (ms)	SD	SE	Mean GoRT	SD	SE
Healthy Controls (N=7)	92.33	8.18	3.09	47.47	5.38	2.03	221.49	53.24	20.12	622.81	166.33	62.87
Patients with SZ or SA (N=6)	89.07	12.31	5.02	52.33	10.9	4.45	381.4	125.7	51.31	732.35	73.64	30.06

Table 5: Between group difference among healthy controls and patients with SZ or SA on the STOP-IT task

Measure	df	t-value	p-value
Go Accuracy	11	0.57	0.58
Stop Accuracy	11	1.33	0.21
SSRT	11	3.08	0.01
GoRT	11	1.49	0.17

Table 6: Demographic profiles of healthy controls and patients with SZ or SA

Characteristics	Patients with SZ or SA (N=3)	Healthy Controls (N=8)	t/χ2	P
Age (years)	43.67	46.13	0.41	0.69
Sex(M/F)	3/0	5/3	2.27	.227
Race(White/Black/Other)	1/1/1	6/2/0	5.09	0.098
Diagnosis(SZ/SA)	3/0	N/A	N/A	N/A
Inpatients/Outpatients	0/3	N/A	N/A	N/A

Table 7: Pre-task RSFC among (R) STN-(R) GP in patients with SZ or SA as compared to controls.

	ROI pair	Mean RSFC	SD	SE	t-value	p-value
Controls	(R) STN-(R)GP	0.3	0.12	0.06	4.85	0.007
Patients	(R) STN-(R)GP	0.08	0.11	0.04		

Table 8: Post-task RSFC between (R) STN-(R) GP among controls and patients with SZ or SA

	ROI pair	Mean RSFC	SD	SE	t-value	p-value
Controls	(R) STN-(R)GP	0.28	0.12	0.05	0.172	0.87
Patients	(R) STN-(R)GP	0.3	0.14	0.07		

Table 9: Comparison of pre-task and post-task RSFC among (R) STN-(R) GP in people with SZ or SA and controls

	ROI pair	Mean RSFC	SD	t-value	p-value
Controls (N=8)	Pre-task (R)STN-(R) GP	0.3	0.12	0.17	0.87
	Post-task (R)STN-(R) GP	0.28	0.11		
Patients (N=3)	Pre-task (R)STN-(R) GP	0.08	0.11	12.13	0.007*
	Post-task (R)STN-(R) GP	0.3	0.14		

*= indicates a significant difference

CHAPTER 5: OVERALL CONCLUSIONS AND FUTURE DIRECTIONS

We conducted a set of studies to assess the functional connectivity among a putative response inhibition network under various conditions: at rest, during task performance and post-task rest and suggest that people with SZ exhibit impaired connectivity among key structures, and this impaired connectivity may have implications on behavioral performance. This observed decrease in connectivity is in further support of previous studies (Woodward et al., 2011; Tu et al., 2010; Li et al., 2010; Kim et al., 2009; Whitfield-Gabriel et al., 2009; Meda et al., 2009; Zhou et al., 2007; Liang et al., 2006; Foucher et al., 2005).

Studies have shown a marked difference in social and cognitive functioning as well as severity of symptoms among inpatients and those treated in outpatient clinics. Outpatient population are more cognitively high functioning (Rosenfeld et al., 1992), are able to maintain social relationships and longer periods of employment (Gandotra et al., 2004) and are more likely to be compliant with their antipsychotic medications, and are less likely than inpatients to discontinue their medication (Ruscher et al., 1997; Garavan et al., 1998). Specifically, both positive and negative psychotic symptoms have been shown to be markedly increased in inpatient vs. outpatient population and the age of onset among the inpatient population is significantly younger than among the outpatient population (Knobler et al., 1999; Perlick et al., 1992). Findings from our study suggest that inpatients exhibited significantly increased positive symptoms on the PANSS when compared to outpatients. Importantly, resting state functional connectivity between bilateral frontal lobes has been shown to be related to psychotic symptoms (Rotarska-Jagiela et al., 2010). However, to date, no studies

have looked at the differential patterns of functional connectivity, either at rest or during task, as a function of this specific type of patient categorization. As such, we further assessed differential patterns of connectivity among the patient subgroups. Our results show that dividing the patient group in this manner may provide us with a better understanding of the various facets of the illness.

The basal ganglia model of response inhibition suggests a key role for subcortical structures such as the thalamus (Thal), the subthalamic nucleus (STN), globus pallidus (GP) and the striatum (ST) in influencing the outcome of motor behavior and our study suggests that dysfunctional connectivity among these regions may impact behavioral performance mediated by the affected regions.

The patient population showed abnormal dysconnectivity among subcortical structures, Thal, STN, GP and the ST, involved in the basal ganglia model of response inhibition, with inpatients showing additional connectivity problems among subcortical structures. Impaired connectivity among the affected structures suggests a net increase in activity of the premotor cortex by the Thal, mediated by decreased inhibition by GP. This impaired connectivity was associated with decreased ability to adequately perform on the stop accuracy component of the SST. Specifically, inpatients show a positive correlation among the FC between ST and GP and stop accuracy such that as the extent of FC among the ST and GP decreases, so do performance on stop accuracy. This

may be attributable to decreased inhibition of the GP by the ST, resulting in a net excitation of the thalamus and the premotor regions.

However, we caution against using the stop accuracy behavioral measures in cases where the task's SSD was dynamically manipulated to yield the observed stop accuracy.

According to the horse-race model, the p(inhibit|signal) decreases as the SSD increases and subjects are more likely to incorrectly respond to the stop stimuli. However, our results indicate otherwise. Both controls and patients showed an increase in stop accuracy above a SSD of 550 ms when compared to below an SSD of 550 ms, suggesting that both group performed better at longer SSDs. This improved performance is reflected in the % of SSD above 550 ms. In controls, 79%, SD=+/- 10.1 of all SSDs were above 550 ms whereas 67.47%, SD= +/- 25.9, of all SSD in patients were above 550 ms. Because the subjects are spending the majority of the time above an SSD of greater than 550 ms (As reflected by the % of SSD above 550 ms) and because their stop performance improves as SSD increases, the task may lack construct validity. This violation of the underlying assumption of the horse-race model makes the resulting stop accuracy measure and the subsequent group comparison invalid.

Additionally, both subject groups showed an increase in go reaction time as a function of SSD, suggesting that they took longer to respond to the go accuracy component of the SST. This increase in go reaction time suggests that the subjects employed a waiting strategy to see if the stop signal would appear before making or withholding a response. This increase in go reaction time might

explain the observation of increased stop accuracy on the SST. Thus, the observed differences in stop accuracy may not reflect a true difference on the groups' ability to correctly withhold a response but rather may reflect their ability to adopt a strategy to perform on the task. Leotti and Wager (2010) have found that strategies such as waiting can influence SST performance.

For these reasons, the use of the adaptive algorithm to make inferences about population performance on the stop accuracy measure is not valid.

Patterns of subcortical dysconnectivity were also observed at rest among the outpatient population. However, this dysconnectivity was less widespread among the outpatient group when compared to the inpatient group. Importantly, after correcting for outliers, we did not observe any significant relationship between functional dysconnectivity among region pairs at rest and any behavioral measures on the SST. So, although they exhibited decreased connectivity at rest, which may be indicative of a lack of "baseline readiness" and integration, they nonetheless performed as well as the controls on the task. Thus, it seems their ability to recruit neural regions necessary for task performance compensates for the decreased coupling observed at rest. This may be because during the course of task performance, outpatients exhibit a normalization of connections and this normalization may account for the observed lack of differences in behavioral performance. Indeed, assessment of functional connectivity during task performance confirmed this expectation. Outpatients showed a normalization of their functional connectivity among all region pairs when compared to healthy controls. The inpatients, however, showed

dysconnectivity among two region pairs: the (R) preSMA-(R)GP and (R)STN-(L)GP, although these did not reach significance and were only trending. This observation of non-significant connectivity may be a result of the relatively small sample size of our inpatient population. Nonetheless, these observed decreases in dysconnectivity during task performance sheds further light on the different patient subgroups. This is because these deficits were only observed among the inpatient population and may reflect additional impairments in their ability to recruit these regions during task performance. If the (R) preSMA-(R) GP had indeed reached significance and if the use of the stop accuracy to make inferences about between group differences in behavior was valid, then the dysconnectivity among this region pair would help explain the observed decrease in performance on the stop accuracy. Although there are no direct connections between the preSMA and the GP, dysconnectivity among these regions might indicate impairment within the mechanism that underlies motor inhibitory control, the preSMA, and its subsequent connections to the GP via the ST (and the net increase in premotor activation). Similarly, an observed interhemispheric dysconnectivity via the corpus callosum between the (R) STN-(L) GP would also result in a net decreased inhibitory effects of GP on the Thal.

Interestingly, changes in the patterns of connectivity were not uniformly observed across subject groups. Patterns of connectivity (from rest to task) among outpatients completely normalized in response to behavioral "interventions," such as performing the SST, whereas inpatients did not show complete normalization. Specifically, when we assessed how the dysconnectivity

patterns that were initially observed during rest changed during task performance, one region pair, (R)STN-(R)GP barely missed significance at p=0.06. This suggests that this region pair, with a larger inpatient sample size, may have exhibited a significant lack of normalization and would help to explain the observation of decreased stop accuracy among the inpatient population.

In healthy controls, functional connectivity among structures has been shown to remain stable across time (Fox & Raichle, 2007) , a phenomenon further supported by our findings. A comparison of resting state connectivity among controls before and after performing the SST indicates stability of the FC. This was not observed among the patient (outpatient population only). They showed a significant increase in their resting connectivity immediately following task performance, suggesting normalization of their baseline connectivity. Unfortunately, because we did not conduct a second behavioral session following the post-task resting state, we are unable to assess its effect on behavioral performance. Additionally, the three patients that participated in this pilot study were all living in an outpatient assisted living facility. Studies have shown a marked difference in social and cognitive functioning as well as severity of symptoms among inpatients and those treated in outpatient clinics (Knobler et al., 1999; Perlick et al., 1992). The data presented earlier (chapters 2 and chapter 3) show that inpatients have additional aberrant functional connectivity when compared to outpatients. Thus, the post-task normalization of RSFC observed in the patient population might be related to the relatively higher functioning and decreased severity of symptoms of the outpatient population.

However, because our patient population did not include inpatients, we were unable to assess whether the post-task normalization was related to illness duration, social functioning or some other factor. Future studies should not only assess whether between subgroup differences in post-task resting state normalization exist, but should also the relative lasting effects of such normalizations.

Additionally, this observation of functional connectivity normalization warrants further research to explore whether such normalizations can be used to test the effects of targeted behavioral therapy on “restoring” neural connectivity.

Studies have consistently shown deficits in homotopic interhemispheric interactions in people with SZ, suggesting impairment in functional integration of the two hemispheres. For example: a study by Mohr et al., (2000) shows that, controls process words more efficiently on conditions where stimuli are presented bilaterally vs. unilaterally. However, patients with impaired hemispheric integration lacked this advantage in bilateral processing. The observed pattern of dysconnectivity in our data set suggests that patients exhibit less interhemispheric integration than controls. Additionally, the patients exhibit dysconnectivity among regions that mediate both the go and the stop process among structures in the basal ganglia model of response inhibition. The preSMA shows strong interconnectivity to the basal ganglia (including the ST and the GP) circuitry of motor control and helps to determine the motor outcome of the go and stop process (Duann et al., 2009). Our patient population showed decreased

connectivity between the preSMA and the GP, suggesting that preSMA isn't adequately mediating motor inhibitory control.

It is important to note that the observation of dysconnectivity has been reported across various disorders, including autism spectrum disorders (Welchew et al., 2005; Koshino et al., 2005; Sundaram et al., 2008), Alzheimer's disease (Stam et al., 2006; Damoiseaux et al., 2009; Caffo et al., 2010), Parkinson's disease (Stoffers et al., 2008), depression (Kenny et al., 2010, Zhang et al., 2011), bipolar disorders (Almeida et al., 2009), obesity (Dubbelink et al., 2008) and drug use (Wilcox et al., 2011). Therefore, dysconnectivity cannot be considered a feature that is unique to SZ, but may be due to some underlying physiological changes common to these disorders. However, it is possible that, although different disorders show dysconnectivity, the *patterns* of dysconnectivity observed might be unique to the disorder. Ongur et al., (2010) studied connectivity patterns within the default mode network in healthy controls, patients with SZ and those with bipolar disorder. Although dysconnectivity was reported in both patient population, the areas that were involved differed significantly between the groups. Further studies that compare the patterns of dysconnectivity across various disorders,and its behavioral impact,is warranted. Doing so would give us a better understanding of the types of mechanisms that may contribute to functional dysconnectivity.

There are a number of limitations to the study which future studies should attempt to address.

First, all patients were receiving antipsychotic medications at the time of the scanning. A review by Davis et al. (2005) suggested that treatment with antipsychotic medications results in normalization of brain functions, so that it is more similar to the brain functions in controls. However, even if treatment with antipsychotics medications were shown to normalize functional connectivity, the presence of observed differences in FC suggests that our results are likely attributable to the disease rather than pharmacological therapy. However, the confounding effects of medication on normalizing functional connectivity cannot be ruled out until future studies with medication-naïve patients are conducted.

Second, we employed a region of interest method to study the functional connectivity. Although this method is strongly hypothesis driven, it has a major limitation—it only shows the connections between regions that were chosen *a priori* and thus doesn't show the mediating effects of a third region. Therefore, the observed lack of dysconnectivity may not necessarily reflect impaired connectivity and may actually recruit significantly more or less of the brain than the previously delineated regions.

Third, we did not assess the structural connectivity among the regions involved in the SST nor did we assess the structural connectivity among the interhemispheric fiber tracts, such as the corpus callosum (CC), anterior commissure (AC) and the posterior commissure (PC). Our results show interferences in interhemispheric connections and assessing the structural connectivity of the CC, AC and PC would shed some light on whether the

decreased connectivity could be attributed to decreased white matter integrity of structures that mediate interhemispheric communications.

Fourth, the use of the use of an adaptive algorithm to make inferences about population performance on the stop accuracy measure is not valid.

The results of this thesis indicate that patients with SZ exhibit impairments in functional connectivity among regions that sub serve the stop signal task and these impairments were observed under both resting and task conditions. This finding is consistent with previous research that shows aberrant functional connectivity in patients with SZ. Although our behavioral data from the SST did not yield the expected results, we have identified a different version of the SST (the STOP-IT) that, according to our pilot data, is sensitive enough to differentiate between group differences in the measure of interest, the SSRT.

Finally, our results give support to a differential pattern of dysconnectivity among the patient population, suggesting that this population should be subdivided into inpatient and outpatient populations. Our results indicate that inpatients exhibit marked decrease in functional connectivity at rest and this dysconnectivity is not overcome during task performance. This pattern was not observed in the outpatient population. Whereas the outpatient population also showed significantly decreased connections during the rest condition, their connectivity patterns normalized during task performance. This suggests that outpatients, who by definition need less intensive care and are thus more self-

sufficient and are less symptomatic, seem to recruit the relevant neural structures enough to perform as well as their healthy counterparts. Similar normalization was observed in the outpatient population in the resting state connectivity immediately following task performance. This observation of functional connectivity normalization warrants further research to explore whether such normalizations can be used to test the effects of targeted behavioral therapy on “restoring” neural connectivity.

References: Chapter 1

Alderson, R. M., Rapport, M. D., & Kofler, M. J. (2007). Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of the stop-signal paradigm. *J.Abnorm.Child Psychol., 35,* 745-758.

Aron, A. R., Dowson, J. H., Sahakian, B. J., & Robbins, T. W. (2003). Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biol.Psychiatry, 54,* 1465-1468.

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans.*Nature Neuroscience, 6,* 115-116.

Aron, A. R. & Poldrack, R. A. (2006). Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J.Neurosci., 26,* 2424-2433.

Aron, A.R. (2010). From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biol Psychiatry, 15*, 55-68.

Ascher-Svanum, H., Nyhuis, A.W., Faries, D.E., Ball, D.E., Kinon, B.J., (2010). Involvement in the US criminal justice system and cost implications for persons treated for schizophrenia. *BMC Psychiatry, 10,* 11.

Badcock, J. C., Michie, P. T., Johnson, L., & Combrinck, J. (2002). Acts of control in schizophrenia: dissociating the components of inhibition. *Psychol.Med., 32,* 287-297.

Baldeweg , T., Wong, D., Stephan, K.E., (2006). Nicotinic modulation of human auditory sensory memory: Evidence from mismatch negativity potentials. *Int J Psychophysiol, 1*, 49-58.

Baldwin, A.E., Sadeghian, K., Kelley, A.E., (2002). Appetitive instrumental learning requires coincident activation of NMDA and dopamine D1 receptors within the medial prefrontal cortex. *J Neurosci, 3,* 1063-71.

Barch, D. M., Carter, C. S., Braver, T. S., Sabb, F. W., MacDonald, A., III, Noll, D. C. et al. (2001). Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. *Arch Gen Psychiatry, 58,* 280-288.

Bekker, E. M., Overtoom, C. C., Kenemans, J. L., Kooij, J. J., De, N., I, Buitelaar, J. K. et al. (2005). Stopping and changing in adults with ADHD. *Psychol.Med., 35,* 807-816.

Bellgrove, M. A., Chambers, C. D., Vance, A., Hall, N., Karamitsios, M., & Bradshaw, J. L. (2006).Lateralized deficit of response inhibition in early-onset schizophrenia.*Psychol.Med., 36,* 495-505.

Bilder, R. M., Goldman, R. S., Robinson, D., Reiter, G., Bell, L., Bates, J. A. et al. (2000). Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am.J.Psychiatry, 157,* 549-559.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995).Functional connectivity in the motor cortex of resting human brain using echo-planar MRI.*Magn Reson.Med., 34,* 537-541.

Black, J.E., Kodish, I.M., Grossman, A.W., Kllinstsova, A.Y., et al., (2004).Pathology of layer V pyramidal neurons in the prefrontal cortex of patients with schizophrenia.*Am J Psychiatry, 4,* 742-4.

Bluhm, R. L., Miller, J., Lanius, R. A., Osuch, E. A., Boksman, K., Neufeld, R. et al. (2007). Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: Anomalies in the default network. *Schizophr.Bull., 33,* 1004-1012.

Boksman, K., Theberge, J., Williamson, P., Drost, D.J., Malla, A. et al., (2005). A 4.0-T fMRI study of brain connectivity during word fluency in first-episode schizophrenia.*Schizophr Res, 75,* 247-63.

Bramon, E., Rabe-Hesketh, S., Sham, P., Murray, R. M., & Frangou, S. (2004). Meta-analysis of the P300 and P50 waveforms in schizophrenia.*Schizophrenia Research.70.(2-3):315.-29.*.

Calicott, J, B.A., Mattay, V., Langheim, F.J.P., Duyn, J., Coppola, R., Goldberg, T., Weinberger, D. (2000). Physiological Dysfunction of the Dorsolateral

Prefrontal Cortex in Schizophrenia Revisited. *Cereb Cortex, 10,* 1078-1092.

Castellanos, F. X., Margulies, D. S., Kelly, C., Uddin, L. Q., Ghaffari, M., Kirsch, A. et al. (2008). Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biol.Psychiatry, 63,* 332-337.

Chambers, C. D., Bellgrove, M. A., Stokes, M. G., Henderson, T. R., Garavan, H., Robertson, I. H. et al. (2006). Executive "brake failure" following deactivation of human frontal lobe. *J.Cogn Neurosci., 18,* 444-455.

Clinton, S. M., Ibrahim, H. M., Frey, K. A., Davis, K. L., Haroutunian, V., & Meador-Woodruff, J. H. (2005). Dopaminergic abnormalities in select thalamic nuclei in schizophrenia: involvement of the intracellular signal integrating proteins calcyon and spinophilin. *Am.J.Psychiatry, 162,* 1859-1871.

Coccaro, E. F. (1996). Neurotransmitter correlates of impulsive aggression in human. *Ann.NY Acad Sci*, *22*, 82-89.

Cordes, D., Haughton, V. M., Arfanakis, K., Carew, J. D., Turski, P. A., Moritz, C. H. et al. (2001). Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data.*AJNR Am.J.Neuroradiol., 22,* 1326-1333.

De Jong, R., Coles, M.G., Logan, G.D., Gratton, G. (1990). In search of the point of noreturn-the control of response processes. *J Exp Psychol Hum Percept Perform 16,* 164.

Di Martino A., Scheres A., Margulies D. S., Kelly A. M., Uddin L. Q., Shehzad Z., Biswal B., Walters J. R., Castellanos F. X., Milham M. P. (2008). Functional connectivity of human striatum: a resting state FMRI study. Cereb.Cortex18, 2735–2747.

Doniger, G.M., Foxe, J.J., Murray, M.M., Higgins, B.A., Snodgrass, J.G., Schroeder, C.E., et al. (2000). Activation time course of ventral visual stream object-recognition areas: high density electrical mapping of perceptual closure processes. *J. Cogn Neurosci, 12*, 615-621.

Duann, J. R., Ide, J. S., Luo, X., & Li, C. S. (2009). Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. *J.Neurosci., 29,* 10171-10179.

Eagle, D.M., Baunez, C., Shahl, A.P., Lehmann, O., Robbins, T.W. (2004). Inhibitory control in rats performing a stop-signal reaction time task: differential effects of lesions of the orbitofrontal cortex, infralimbic cortex and subthalamic nucleus. *Soc Neurosci Abstr, 30*, 781-12.

Egan, M. F., Straub, R. E., Goldberg, T. E., Yakub, I., Callicott, J. H., Hariri, A. R. et al. (2004). Variation in GRM3 affects cognition, prefrontal glutamate, and risk for schizophrenia. *Proc.Natl.Acad.Sci.U.S.A, 101,* 12604-12609.

Fox, M. D. & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat.Rev.Neurosci., 8,* 700-711.

Franke, C., Reuter, B., Schulz, L., & Kathmann, N. (2007). Schizophrenia patients show impaired response switching in saccade tasks. *Biol.Psychol., 76,* 91-99.

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping, 2,* 56-78.

Friston, K.J., Frith, C.D., (1995). Schizophrenia: a disconnection syndrome? *Clin Neurosci, 3,* 89-97.

Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., et al., (1997).Psychophysiological and modulatory interactions in neuroimaging.*NeuroImage, 6,* 218-229.

Friston, K. J. (1998). The disconnection hypothesis.*Schizophrenia Research, 30,* 115-125.

Garey, L.J., Ong, W. Y., Patel, T.S., Kanani, M., Davis, A., et al., (1998).Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia, *J Neurol Neurosurg Psychiatry,4*, 446-53.

Garrido, M.I., Kilner, J.M., Stephan, K.E., Friston, K.J., (2009). The mismatch negativity: a review of underlying mechanisms. *Clin Neurophysiol, 3,* 453-63.

Garrity, A. G., Pearlson, G. D., McKiernan, K., Lloyd, D., Kiehl, K. A., & Calhoun, V. D. (2007). Aberrant "default mode" functional connectivity in schizophrenia.*Am.J.Psychiatry, 164,* 450-457.

Gauggel, S., Rieger, M., Feghoff, T.A. (2004).Inhibition of ongoing responses in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry, 75,* 539-544.

Gitelman, D.R., Penny, W.D., Ashburner, J., Friston, K.J., (2003). Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution.Neuroimage, 1, 200-7.

Gopal, Y. V., Variend, H.A. (2005). First-episode schizophrenia: review of cognitive deficits and cognitive remediation. *Adv Psychiatr Treat*, *11,* 38-44.

Green, M.F., (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder.*J Clin Psychiatry, 67,* e12.

Hampshire, A., Chamberlain, S.R., Monti, M.M.,Duncan, J., Owen, A.M., (2010). The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage, 50,1313-1319.*

Harrison, P.J., Weinberger, D.R., (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry, 1*, 40-68.

Harrison, P.J., Law, A.J., Eastwood, S.L. (2003). Glutamate receptors and transporters in the hippocampus in schizophrenia.*Ann N Y Acad Sci, 1003,* 94-101.

Harvey, P.D., Doherty, N.M., Serper, M.R., & Rasmussen, M. (1990). Cognitive deficits and thought disorder: An 8-month follow up study. *Schizophrenia Bulletin,* 16, 147-156.

He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron, 53,* 905-918.

Hill, S. K., Schuepbach, D., Herbener, E. S., Keshavan, M. S., & Sweeney, J. A. (2004).Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naive patients with schizophrenia.*Schizophr.Res., 68,* 49-63.

Hoffman, R.E., Buchsbaum, M.S., Escobar, M.D., Makuch, R.W., Nuechterlein, K.H., Guich, S.M. (1991) EEG coherence of prefrontal areas in normal and schizophrenic males during perceptual activation. *J Neuropsychiatry Cli Neurosci,* 3,169 –175.

Hoptman, M.J., Volavka, J., Johnson, G., Weiss, E., Bilder, R.M., and Lim, K.O. (2002). Frontal White Matter Microstructure, Aggression, and Impulsivity in Men with Schizophrenia: A Preliminary Study. *Biological Psychiatry, 52,* 9-14.

Hoptman, M.J. (2003). Neuroimaging studies of violence and antisocial behavior. *J Psychiatric Pract, 9,*265–278.

Hoptman, M. J., Ardekani, B. A., Butler, P. D., Nierenberg, J., Javitt, D. C., & Lim, K. O. (2004). DTI and impulsivity in schizophrenia: A first voxelwise correlational study. *NeuroReport, 15,* 2467-2470.

Hoptman, M. J. & Nolan, K. A. (2009).The role of prefrontal abnormalities in schizophrenia. In D.C.Javitt & J. T. Kantrowitz (Eds.), *Schizophrenia* (pp. 384-401). New York: Springer.

Huddy, V. C., Aron, A. R., Harrison, M., Barnes, T. R., Robbins, T. W., & Joyce, E. M. (2009).Impaired conscious and preserved unconscious inhibitory processing in recent onset schizophrenia.*Psychol.Med., 39,* 907-916.

Huizenga, H. M., van Bers, B. M., Plat, J., van den Wildenberg, W. P., & van der Molen, M. W. (2009). Task complexity enhances response inhibition deficits in childhood and adolescent attention-deficit/hyperactivity disorder: a meta-regression analysis. *Biol.Psychiatry, 65,* 39-45.

IversenSD, Mishkin M (1970) Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Exp Brain Res, 11,* 376–386.

Javitt, D.C., Balla, A., Burch, S., (2004).Reversal of phencyclidine-induced dopaminergic dysregulation by N-methyl-D-aspartate receptor/glycine-site agonists.*Neuropsychopharmacology, 2,* 300-7.

Javitt, D.C., (2007). Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. *Int Rev Neurobiol, 78,* 69-108.

Kaladjian, A., Jeanningros, R., Azorin, J. M., Grimault, S., Anton, J. L., & Mazzola-Pomietto, P. (2007).Blunted activation in right ventrolateral prefrontal cortex during motor response inhibition in schizophrenia.*Schizophr.Res., 97,* 184-193.

Kay, S.R., Murrill, L.M., (1990). Predicting outcome of schizophrenia: significance of symptoms profiles and outcome dimensions.*Compr Psychiatry, 2,* 91-102.

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kamyema, M., & Mihashita, Y. (1999).Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI.*Brain, 122,* 981-991.

Kooijmans, R., Scheres, A., & Oosterlaan, J. (2000). Response inhibition and measures of psychopathology: a dimensional analysis. *Child Neuropsychol., 6,* 175-184.

Kraus, M. S. & Keefe, R. S. (2007).Cognition as an outcome measure in schizophrenia.*Br.J.Psychiatry Suppl, 50,* s46-s51.

Laufs, H., Krakow, K., Sterzer, P., Eger, E., Beyerle, A., Salek-Haddadi, A. et al. (2003).Electroencephalographic signatures of attentional and cognitive

default modes in spontaneous brain activity fluctuations at rest.*Proc.Natl.Acad.Sci.U.S.A, 100,* 11053-11058.

Lewis, D.A, Lieberman, J.A. (2000).Catching up on schizophrenia: natural history and neurobiology.*Neuron*, *28*, 325–334.

Li, C. S., Yan, P., Sinha, R., & Lee, T. W. (2008). Subcortical processes of motor response inhibition during a stop signal task. *NeuroImage, 41,* 1352-1363.

Liang, M., Zhou, Y., Jiang, T., Liu, Z., Tian, L., Liu, H. et al. (2006).Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging.*NeuroReport, 17,* 209-213.

Liddle, P. F., Kiehl, K. A., & Smith, A. M. (2001).Event-related fMRI study of response inhibition.*Human Brain Mapping, 12,* 100-109.

Lim, K.O., Hedehus, M., Moseley, M., Crespigny, A., Sullivan, E.V., et al. (1999). Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Arch Gen Psychiatry, 56,* 367-374.

Lipszyc, J. & Schachar, R. (2010). Inhibitory control and psychopathology: A meta-analysis of studies using the stop signal task. *J.Int.Neuropsychol.Soc.,* 1-13.

Liu, H., Liu, Z., Liang, M., Hao, Y., Tan, L., Kuang, F., Yi, Y., Xu, L., Jiang, T (2006). Decreased regional homogeneity in schizophrenia: a resting state functional magnetic resonance imaging study. *Neuroreport, 17,* 19-22.

Logan, G.D., Cowan, W.B., Davis, K.A. (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method.*J Exp Psychol Hum Percept Perform, 2,* 276-91.

Logan, G. D. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In D.Dagenbach & T. H. Carr (Eds.), *Inhibitory processes in attention, memory, and language* (pp. 675-691). San Diego, CA: Academic Press.

Mahurin, R.K., Velligan, D.I., Miller, A.L., (1998). Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. *Psychiatry Res, 2,*139-49.

Margulies, D. S., Kelly, A. M., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2007). Mapping the functional connectivity of anterior cingulate cortex.*NeuroImage, 37,* 579-588.

McAlonan, G. M., Cheung, V., Chua, S. E., Oosterlaan, J., Hung, S. F., Tang, C. P. et al. (2009). Age-related grey matter volume correlates of response inhibition and shifting in attention-deficit hyperactivity disorder. *Br.J Psychiatry, 194,* 123-129.

McEvoy, J.P. (2007). The costs of schizophrenia.*J Clin Psychiatry, 68,* 4-7.

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., & Reiss, A. L. (2001). Error-related brain activation during a go/nogo response inhibition task. *Human Brain Mapping, 12,* 131-143.

Meyer-Lindenberg, A., Poline, J. B., Kohn, P. D., Holt, J. L., Egan, M. F., Weinberger, D. R. et al. (2001). Evidence for abnormal cortical functional connectivity during working memory in schizophrenia.*Am.J.Psychiatry, 158,* 1809-1817.

Monfils, M.H., Teskey, G.C., (2004). Induction of long-term depression is associated with decreased dendritic length and spine density in layers III and V of sensorimotor neocortex. *Synapse, 2,* 114-21.

Nolan, K., D'Angelo, D., Hoptman, M.J., (2011). Self-report and laboratory measures of impulsivity in patients with schizophrenia or schizoaffective disorder and healthy controls. *Psychiatry Research, 187,* 301-303.

McGurk, S. R. (1999). The effects of clozapine on cognitive functioning in schizophrenia.*J.Clin.Psychiatry, 60 Suppl 12,* 24-29.

Mink, J.W. (1996). The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol, 50*, 381– 425.

Nambu, A., Tokuno, H., Takada, M. (2002).Functional significance of the corticosubthalamo-pallidal "hyperdirect" pathway.*Neurosci Res, 43*,111–117.

Osman, A., Kornblum, S., & Meyer, D. E. (1986). The point of no return in choice reaction time: Controlled and ballistic stages of response preparation. *Journal of Experimental Psychology: Human Perception and Performance, 12,* 243-258.

Osman, A., Kornblum, S., & Meyer, D. E. (1990). Does motor programming necessitate response execution? *Journal of Experimental Psychology: Human Perception and Performance, 16,* 183-198.

Perlstein, W. M., Dixit, N. K., Carter, C. S., Noll, D. C., & Cohen, J. D. (2003). Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biol.Psychiatry, 53,* 25-38.

Raichle, M. E. (2001). Cognitive neuroscience.Bold insights.*Nature, 412,* 128-130.

Raichle, M.E., Mintun, M.A., (2006).Brain work and brain imaging.*Annu Rev Neurosci, 29,* 449-76.

Rasser, P.E., Schall, U., Todd, J., Michie, P.T., Ward, P.B., et al., (2011). Gray matter deficits, mismatch negativity and outcomes in schizophrenia. *Schizophrenia Bull, 37,* 131-140.

Riecher-Rossler A. (2002). Estrogen effects in schizophrenia and their potential therapeutic implications: review. *Arch Women's Mental Health, 5,* 111-118.

Rieger, M., Gauggel, S., Burmeister, K., (2003).Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. *Neuropsychology, 17,* 272-282.

Robins, L.N., Locke, B.Z., & Regier, D.A. (1991).An overview of psychiatric disorders in America. In Psychiatric Disorders in America: The Epidemiologic Catchment Area Study, 328-366. Free Press: New York.

Rubia, K., Smith, A.B., Brammer, M.J., Taylor, E., (2003). Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible -for error detection. *Neuroimage, 20,* 351-8.

Sagaspe, P., Philip, P., Schwartz, S., Inhibitory motor control in apneic and insomniac patients: a stop task study. *J Sleep Res, 16,* 381-7.

Salisbury, D.F., Shenton, M.E., Griggs, C.B., Bonner-Jackson, A., McCarley, M.D., (2002). Mismatch Negativity in Chronic Schizophrenia and First-Episode Schizophrenia. *Arch Gen Psychiatry,* 59, 686-694.

Sehatpour, P., Molholm, S., Schwartz, T.H., Mahoney J.R., Mehta, A.D. et al. (2008).A human intracranial study of long-range oscillatory coherence across a frontal-occipital-hippocampal brain network during visual object processing.*PNAS, 105,* 4399-4404.

Smith-Roe, S.L., Kelley, A.E., (2000).Coincident activation of NMDA and dopamine D1 receptors within the nucleus accumbens core is required for appetitive instrumental learning. *J Neuroscience, 20,* 7737-42.

Stephan, K., Baldeweg, T., Friston, K. (2006).Synaptic plasticity and dysconnection in schizophrenia.*Biological Psychiatry, 59*, 929-939.

Stephan, K., Friston, K., Frith, C., (2009). Dysconnectivity in schizophrenia: from abnormal synaptic plasticity to failures of self monitoring. *Schizophrenia Bulletin, 35,* 509-527.

Thoma, P., Wiebel, B., & Daum, I. (2007). Response inhibition and cognitive flexibility in schizophrenia with and without comorbid substance use disorder. *Schizophr.Res., 92,* 168-180.

Tu, P., Buckner, R.L., Zollei, L., Dyckman, K.A. et al., (2010). Reduced functional connectivity in a
right-hemisphere network for volitional ocular motor control in schizophrenia. *Brain, 133,* 625–637.

Twamley, E.W., Palmer, B.W., Jeste, D.V., Taylor, M.J., Heaton, R.K., (2006). Transient and executive function working memory in schizophrenia.*Schizophr Res, 87,* 85-90.

Umbricht, D., Schmid, L., Koller, R., Vollenweider, F. X., Hell, D., & Javitt, D. C. (2000). Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Archives of General Psychiatry, 57,* 1139-1147.

Velligan, D. & Alphs L. (2008). Negative Symptoms in Schizophrenia: The Importance of Identification and Treatment. *Psychiatric Times* , 3, 25.

Verbruggen, F. & Logan, G. D. (2008).Response inhibition in the stop-signal paradigm.*Trends Cogn Sci., 12,* 418-424.

Volkow, N. D., Wolf, A. P., Brodie, J. D., Cancro, R., Overall, J. E., Rhoades, H. et al. (1988).Brain interactions in chronic schizophrenics under resting and activation conditions.*Schizophr Res., 1,* 47-53.

Wardak, C., (2011). The Role of the Supplementary Motor Area in Inhibitory Control in Monkeys and Humans. The Journal of Neuroscience, 31, 5181–5183.

Wang L, Yu C, Chen H, Qin W, He Y, Fan F, et al. (2010). Dynamic functional reorganization of the motor execution network after stroke.*Brain, 133,* 1224–38.

Weisbrod, M., Kiefer, M., Marzinzik, F., & Spitzer, M. (2000). Executive control is disturbed in schizophrenia: evidence from event-related potentials in a Go/NoGo task. *Biological Psychiatry.47.(1):51.-60.*

Wolf, D. H., Gur, R. C., Valdez, J. N., Loughead, J., Elliott, M. A., Gur, R. E. et al. (2007). Alterations of fronto-temporal connectivity during word encoding in schizophrenia.*Psychiatry Res., 154,* 221-232.

Wolf, R.C., Vasic, N., Sambataro, F., Hose, A., Frasch, K., et al., (2009). Temporally anticorrelated brain networks during working memory performance reveal aberrant prefrontal and hippocampal connectivity in patients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry, 8,* 1464-73.

Wu, E. (2005). The Economic Burden of Schizophrenia in the United States in 2002.*J Clin Psychiatry, 66,* 1122-1129.

Zandbelt, B. B. & Vink, M. (2010).On the role of the striatum in response inhibition.*PLoS One, 5,* e13848.

Zhou, Y., Liang, M., Jiang, T., Tian, L., Liu, Y., Liu, Z. et al. (2007).Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI.*Neurosci.Lett., 417,* 297-302.

References: Chapter 2

Aron, A. R. & Poldrack, R. A. (2006). Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J.Neurosci., 26,* 2424-2433.

Beckmann, C. F., Jenkinson, M., Woolrich, M. W., Behrens, T. E., Flitney, D. E., Devlin, J. T. et al. (2006).Applying FSL to the FIAC data: model-based and model-free analysis of voice and sentence repetition priming.*Hum.Brain Mapp., 27,* 380-391.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995).Functional connectivity in the motor cortex of resting human brain using echo-planar MRI.*Magn Reson.Med., 34,* 537-541.

Biswal, B., Mennes, M., Zuo, X. N., Gohel, S., Kelly, C., Smith, S. et al. (2010). Towards Discovery Science of Human Brain Function: The '1000 Connectomes' Project. *Proceedings of the National Academy of Sciences, USA, 107,* 4734-4739.

Cordes, D., Haughton, V. M., Arfanakis, K., Carew, J. D., Turski, P. A., Moritz, C. H. et al. (2001). Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data.*AJNR Am.J.Neuroradiol., 22,* 1326-1333.

Davis, C.E., Jeste, D.V., Eyler, L.T. (2005). Review of longitudinal functional neuroimaging studies of drug treatments in patients with schizophrenia. *Schizophr Res, 78,* 45–60.

Duann, J. R., Ide, J. S., Luo, X., & Li, C. S. (2009). Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. *J.Neurosci., 29,* 10171-10179.

Fox, M. D., Snyder, A. Z., Zacks, J. M., & Raichle, M. E. (2006). Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat.Neurosci., 9,* 23-25.

Friston, K.J., Frith, C.D., (1995). Schizophrenia: a disconnection syndrome? *Clin Neurosci, 3,* 89-97.

Hill, S. K., Schuepbach, D., Herbener, E. S., Keshavan, M. S., & Sweeney, J. A. (2004).Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naive patients with schizophrenia.*Schizophr.Res., 68,* 49-63.

Honey, G.D., Pomarol-Clotet, E., Corlett, P.R., Honey, R.A., McKenna, P.J., Bullmore, E.T., Fletcher, P.C. (2005) Functional dysconnectivity in schizophrenia associated with attentional modulation of motor function. *Brain, 128*, 2597–2611.

Hoptman, M. J. & Antonius, D. (2011). Neuroimaging correlates of aggression in schizophrenia: An update. *Current Opinion in Psychiatry, 24,* 100-106.

Kerssens, C., Hamann, S., Peltier, S., Hu, X.P., Byas-Smith, M.G., Sebel, P.S (2005).Attenuated Brain Response to Auditory Word Stimulation with Sevoflurane: A Functional Magnetic Resonance Imaging Study in Humans.*Anesthesiology, 103,*11–19.

Knobler, H.Y, Ben Ami, D., Intrator, O., Katz, S., Moshe, D., Lerner, Y. (1999).Symptom severity among chronic schizophrenics in hospital and in the community.*Harefuah, 137, 2*84-7.

Leotti, L.A., Wager, T.D. (2010). Motivational influences on response inhibition measures. *Journal of Exp Psy, 36,* 430-447.

Liddle, P. F., Kiehl, K. A., & Smith, A. M. (2001).Event-related fMRI study of response inhibition.*Human Brain Mapping, 12,* 100-109.

Lipszyc, J. & Schachar, R. (2010). Inhibitory control and psychopathology: A meta-analysis of studies using the stop signal task. *J.Int.Neuropsychol.Soc.,* 1-13.

Lowe, M. J., Mock, B. J., & Sorenson, J. A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations.*NeuroImage, 7,* 119-132.

Mostofsky, S. H., Schafer, J. G., Abrams, M. T., Goldberg, M. C., Flower, A. A., Boyce, A. et al. (2003). fMRI evidence that the neural basis of response inhibition is task-dependent. *Brain Res.Cogn Brain Res., 17,* 419-430.

Nolan, K., D'Angelo, D., Hoptman, M.J., (2011). Self-report and laboratory measures of impulsivity in patients with schizophrenia or schizoaffective disorder and healthy controls. *Psychiatry Research, 187,* 301-303.

Perlick, D., Stastny, P., Mattis, S., and Teresi, J. (1992).Contribution of family, cognitive, and clinical dimensions to long term outcome in schizophrenia.*Schizophrenia Research,*6, 257-265.

Rotarska-Jagiela, A., van de Ven, V., Oertel-Knöchel, V., Uhlhaas, P.J., Vogeley, K., Linden, D.E. (2010). Resting-state functional network correlates of psychotic symptoms in schizophrenia.*Schizophrenia Research, 1,*21-30.

Stephan, K., Baldeweg, T., Friston, K. (2006).Synaptic plasticity and dysconnection in schizophrenia.*Biological Psychiatry, 59*, 929-939.

Stephan, K.E., Friston, K.J., Frith, C.D., (2009). Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring*. Schizophr Bull, 35*, 509–27.

Teplin, L. A., Abram, K. M., McClelland, G. M., Washburn, J. J., & Pikus, A. K. (2005). Detecting mental disorder in juvenile detainees: who receives services.*Am.J.Public Health, 95,* 1773-1780.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N. et al. (2002).Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain.*NeuroImage, 15,* 273-289.

Vincent, J. L., Patel, G. H., Fox, M. D., Snyder, A. Z., Baker, J. T., Van, E. et al. (2007). Intrinsic functional architecture in the anaesthetized monkey brain.*Nature, 447,* 83-86.

Walsh, E., Buchanan, A., & Fahy, T. (2002). Violence and schizophrenia: examining the evidence. *Br.J.Psychiatry, 180,* 490-495.

White, L., Knobler, H.Y., Losonczy, M.F., Keefe, R.S.E., Kate, S., and Frecska,E. (1995). Severity of symptoms in geriatric chronically institutionalized schizophrenic patients. *American Journal of Psychiatry, 152,* 197-207.

Xiong, J., Parsons, L.M., Gao, J.H., Fox, P.T. (1999). Interregional connectivity to primary motor cortex revealed using MRI resting state images. *Hum Brain Mapp, 8,*151–156.

References: Chapter 3

Aron, A. R. & Poldrack, R. A. (2006). Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J.Neurosci., 26,* 2424-2433.

Beckmann, C., Jenkinson, M., & Smith, S. M. (2003).General multi-level linear modelling for group analysis in fMRI.*NeuroImage, 20,* 1052-1063.

Boksman, K., Theberge, J., Williamson, P., Drost, D.J., Malla, A. et al., (2005). A 4.0-T fMRI study of brain connectivity during word fluency in first-episode schizophrenia.*Schizophr Res, 75,* 247-63.

Broyd, S. J.,Demanuele, C., Debener, S., Helps, S., K.; J., Sonuga-Barke, C.J., et al., (2009). Default-mode brain dysfunction in mental disorders: A systematic review. *Neuroscience & Biobehavioral Reviews, 33,* 279–96

Calicott, J, B.A., Mattay, V., Langheim, F.J.P., Duyn, J., Coppola, R., Goldberg, T., Weinberger, D. (2000). Physiological Dysfunction of the Dorsolateral Prefrontal Cortex in Schizophrenia Revisited. *Cereb Cortex, 10,* 1078-1092.

Cox, R.W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29,* 162-173.

Davis, C.E., Jeste, D.V., Eyler, L.T. (2005). Review of longitudinal functional neuroimaging studies of drug treatments in patients with schizophrenia. *Schizophr Res,* 78, 45–60.

Duann, J. R., Ide, J. S., Luo, X., & Li, C. S. (2009). Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. *J.Neurosci., 29,* 10171-10179.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Van Essen, D.C., Raichle, M.E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci, 102,* 9673-9678.

Fox, M. D. & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat.Rev.Neurosci., 8,* 700-711.

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping, 2,* 56-78.

Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., (1997). Psychophysiological and modulatory interactions in neuroimaging.*Neuroimage, 6*, 218-229.

Gitelman, D.R., Penny, W.D., Ashburner, J., Friston, K.J., (2003). Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. Neuroimage, 1, 200-207.

Honey, G.D., Pomarol-Clotet, E., Corlett, P.R., Honey, R.A., McKenna, P.J.,Bullmore, E.T., Fletcher, P.C. (2005) Functional dysconnectivity in schizophrenia associated with attentional modulation of motor function. *Brain, 128*, 2597–2611.

http://www.fmrib.ox.ac.uk/fsl. Retrieved October 17, 2011.

Javitt, D.C., Zukin, S.R. (1991). Recent advances in the phencyclidine model of sczhizophrenia. *Am J Psychiatry, 148.*1301-1308.

Kerssens, C., Hamann, S., Peltier, S., Hu, X.P., Byas-Smith, M.G., Sebel, P.S (2005).Attenuated Brain Response to Auditory Word Stimulation with Sevoflurane: A Functional Magnetic Resonance Imaging Study in Humans.*Anesthesiology,* 103, 11–19.

Knobler, H.Y, Ben Ami, D., Intrator, O., Katz, S., Moshe, D., Lerner, Y. (1999).Symptom severity among chronic schizophrenics in hospital and in the community.*Harefuah, 137,* 284-7.

Liddle, P. F., Kiehl, K. A., & Smith, A. M. (2001).Event-related fMRI study of response inhibition.*Human Brain Mapping, 12,* 100-109.

Logan, G.D., Cowan, W.B., Davis, K.A. (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform, 2,* 276-91.

Logan, G. D. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In D.Dagenbach & T. H. Carr (Eds.), *Inhibitory processes in attention, memory, and language* (pp. 675-691). San Diego, CA: Academic Press.

Meyer-Lindenberg, A., Poline, J. B., Kohn, P. D., Holt, J. L., Egan, M. F., Weinberger, D. R. et al. (2001). Evidence for abnormal cortical functional

connectivity during working memory in schizophrenia.*Am.J.Psychiatry, 158,* 1809-1817.

Mostofsky, S. H., Schafer, J. G., Abrams, M. T., Goldberg, M. C., Flower, A. A., Boyce, A. et al. (2003). fMRI evidence that the neural basis of response inhibition is task-dependent. *Brain Res.Cogn Brain Res., 17,* 419-430.

Nolan, K., D'Angelo, D., Hoptman, M.J., (2011). Self-report and laboratory measures of impulsivity in patients with schizophrenia or schizoaffective disorder and healthy controls. *Psychiatry Research, 187,* 301-303.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., et al. (2001).A default mode of brain function.*Proceedings of the Nat Aca of Sci, 98,* 676-682.

Rorden, C., *MRIcro.* Retrieved October 17, 2011, from http://www.cabiatl.com/mricro/

Stephan, K., Baldeweg, T., Friston, K. (2006).Synaptic plasticity and dysconnection in schizophrenia.*Biological Psychiatry, 59*, 929-939.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N. et al. (2002).Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain.*NeuroImage, 15,* 273-289.

Wardak, C., (2011). The Role of the Supplementary Motor Area in Inhibitory

Control in Monkeys and Humans. The Journal of Neuroscience, 31, 5181–5183.

Woolrich, M. W., Behrens, T. E. J., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004).Multi-level linear modelling for fMRI group analysis using Bayesian inference.*NeuroImage, 21,* 1732-1747.

Worsley, K. (2001). Statistical analysis of activation images. In P.Jezzard, P. M. Matthews, & S. M. Smith (Eds.), Functional MRI: An introduction to methods. Oxford, UK: OxfordUniversity Press.

References: Chapter 4

Alderson, R. M., Rapport, M. D., & Kofler, M. J. (2007). Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of the stop-signal paradigm. *J.Abnorm.Child Psychol., 35,* 745-758.

Aron, A. R. & Poldrack, R. A. (2006). Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J.Neurosci., 26,* 2424-2433.

Bedwell, J.S., Brown, J.M., Miller, S. (2003). The magnocellular visual system and schizophrenia: what can the color red tell us? *Schizophrenia Research, 63,* 273-284.

Bekker, E. M., Overtoom, C. C., Kenemans, J. L., Kooij, J. J., De, N., I, Buitelaar, J. K. et al. (2005). Stopping and changing in adults with ADHD. *Psychol.Med., 35,* 807-816.

Bellgrove, M. A., Chambers, C. D., Vance, A., Hall, N., Karamitsios, M., & Bradshaw, J. L. (2006).Lateralized deficit of response inhibition in early-onset schizophrenia.*Psychol.Med., 36,* 495-505.

Biswal, B., Mennes, M., Zuo, X. N., Gohel, S., Kelly, C., Smith, S. et al. (2010). Towards Discovery Science of Human Brain Function: The '1000 Connectomes' Project. *Proceedings of the National Academy of Sciences, USA, 107,* 4734-4739.

Butler, P.D., Schechter, I., Zemon, V., Schwartz, S.G., Greenstein, V.C., et al. (2001). Dysfunction of early-stage visual processing in schizophrenia.*Am. J, Psychiatry, 158,* 1126-1133.

Cabel, D.W.J., Armstrong, I.T., Reingold, E., Munoz, D.P. (2000) Control of saccadic initiation in a countermanding task using visual and auditory stop signals. *Exp Brain Res, 133,* 431-441

Davis, C.E., Jeste, D.V., Eyler, L.T. (2005). Review of longitudinal functional neuroimaging studies of drug treatments in patients with schizophrenia. *Schizophr Res,* 78*,* 45–60.

Fox, M. D. & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci., 8,* 700-711.

Gauggel, S., Rieger, M., Feghoff, T.A. (2004).Inhibition of ongoing responses in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry, 75,* 539-544*.*

Shannon, B, Raichle, M.E., Snyder, A.Z., Fair, D.A., Mills, K.L., et al., (2011). Premotor functional connectivity predicts impulsivity in juvenile offenders. *Proc Natl Acad Sci U.S, 108,* 11241–11245.

Huddy, V. C., Aron, A. R., Harrison, M., Barnes, T. R., Robbins, T. W., & Joyce, E. M. (2009).Impaired conscious and preserved unconscious inhibitory processing in recent onset schizophrenia.*Psychol.Med., 39,* 907-916.

Huizenga, H. M., van Bers, B. M., Plat, J., van den Wildenberg, W. P., & van der Molen, M. W. (2009). Task complexity enhances response inhibition deficits in childhood and adolescent attention-deficit/hyperactivity disorder: a meta-regression analysis. *Biol.Psychiatry, 65,* 39-45.

James A, Lu Z-L, VanMeter J, Sathian K, Sathian M, Hu X, et al. (2009).Changesin resting state effective connectivity in the motor network followingrehabilitation of upper extremity poststroke paresis.*Topics StrokeRehab, 16*, 270-281.

Kerssens, C., Hamann, S., Peltier, S., Hu, X.P., Byas-Smith, M.G., Sebel, P.S (2005).Attenuated Brain Response to Auditory Word Stimulation with Sevoflurane: A Functional Magnetic Resonance Imaging Study in Humans. *Anesthesiology,* 103, 11–19.

Knobler, H.Y, Ben Ami, D., Intrator, O., Katz, S., Moshe, D., Lerner, Y. (1999).Symptom severity among chronic schizophrenics in hospital and in the community.*Harefuah, 137,* 284-7.

Kooijmans, R., Scheres, A., & Oosterlaan, J. (2000). Response inhibition and measures of psychopathology: a dimensional analysis. *Child Neuropsychol., 6,* 175-184.

Li, C. S., Milivojevic, V., Kemp, K., Hong, K., & Sinha, R. (2006). Performance monitoring and stop signal inhibition in abstinent patients with cocaine dependence. *Drug Alcohol Depend., 85,* 205-212.

Logan, G.D., Cowan, W.B., Davis, K.A. (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform, 2,* 276-91.

Logan, G. D. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In D.Dagenbach & T. H. Carr (Eds.), *Inhibitory processes in attention, memory, and language* (pp. 675-691). San Diego, CA: Academic Press.

McAlonan, G. M., Cheung, V., Chua, S. E., Oosterlaan, J., Hung, S. F., Tang, C. P. et al. (2009). Age-related grey matter volume correlates of response inhibition and shifting in attention-deficit hyperactivity disorder. *Br.J Psychiatry, 194,* 123-129.

McCabe, C., Mishor, Z., Filippini, N., Cowen, P.J., Taylor, M.J & Harmer, C.J. (2011).SSRI administration reduces resting state functional connectivity in dorso-medial prefrontal cortex*. Molecular Psychiatry,16,* 592-594.

Park, C.H., Chang, W.H., Ohn, SH., Kim, S.T., Bang, O.Y., et al., (2011). Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. *Stroke, 42,* 1357-1362.

Perlick, D., Stastny, P., Mattis, S., and Teresi, J. (1992).Contribution of family, cognitive, and clinical dimensions to long term outcome in schizophrenia.*Schizophrenia Research,*6, 257-265.

Rieger, M., Gauggel, S., Burmeister, K., (2003).Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. *Neuropsychology, 17,* 272-282.

Sagaspe, P., Philip, P., Schwartz, S., Inhibitory motor control in apneic and insomniac patients: a stop task study. *J Sleep Res, 16,* 381-7.

Teplin, L. A., Abram, K. M., McClelland, G. M., Washburn, J. J., & Pikus, A. K. (2005). Detecting mental disorder in juvenile detainees: who receives services.*Am.J.Public Health, 95,* 1773-1780.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N. et al. (2002).Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain.*NeuroImage, 15,* 273-289.

Verbruggen, F., Logan, G. D., & Stevens, M. A. (2008). STOP-IT: Windows executable software for the stop-signal paradigm. *Behav.Res.Methods, 40,* 479-483.

Vincent, J. L., Patel, G. H., Fox, M. D., Snyder, A. Z., Baker, J. T., Van, E. et al. (2007). Intrinsic functional architecture in the anaesthetized monkey brain.*Nature, 447,* 83-86.

Walsh, E., Buchanan, A., & Fahy, T. (2002). Violence and schizophrenia: examining the evidence. *Br.J.Psychiatry, 180,* 490-495.

References: Chapter 5

Aron, A. R. & Poldrack, R. A. (2006). Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J.Neurosci., 26,* 2424-2433.

Bluhm, R. L., Miller, J., Lanius, R. A., Osuch, E. A., Boksman, K., Neufeld, R. et al. (2007). Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: Anomalies in the default network. *Schizophr.Bull., 33,* 1004-1012.

Caffo, B., Crainiceanu, C., Verduzco, G., Mostofsky, S., Bassett, S., and Pekar, J. (2010). Two-stage decompositions for the analysis of functional connectivity for fMRI with application to Alzheimer's disease risk. *Neuroimage, 51,* 1140-1149.

Cannon, T. D. (2008). Neurodevelopment and the transition from schizophrenia prodrome to schizophrenia: research imperatives. *Biol. Psychiatry, 64,* 737-738.

Crossley, N.A., Mechelli, A., Fusar-Poli, P., Broome, M.R., Matthiasson, P., et al., (2009).Superiortemporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. *Hum.Brain Mapp. 30,*4129–4137.

Damoiseaux, J.S., Smith, S.M., Witter, M.P., Sanz-Arigita,, E.J., Barkhof, F., et al., (2009). White matter tract integrity in aging and Alzheimer's disease. *Human Brain Mapping, 30,* 1051–1059.

De Almeida, K.M., De Macedo-Soares, M.B., Issler, C.K., Amaral, J.A., Caetano, S. et al., (2009). Obesity and metabolic syndrome in Brazilian patients with bipolar disorder. *Neuropsychiatric, 21,* 84–88.

Duann, J. R., Ide, J. S., Luo, X., & Li, C. S. (2009). Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. *J.Neurosci., 29,* 10171-10179.

Dubbelink, K. T. E., Felius, A., Verbunt, J. P. A., Van Dijk, B. W., Berendse, H. W., Stam, C. J., & Delemarre-Van De Waal, H. A. (2008). Increased Resting-State Functional Connectivity in Obese Adolescents; A Magnetoencephalographic Pilot Study. *PLoS ONE*, *3*, 6.

Foucher, J.R., Vidailhet, P., Chanraud, S., Gounot, D., Grucker, D., et al., (2005). Functional integration in schizophrenia: too little or too much? preliminary results on fMRI data. *Neuroimage, 26,* 374–388.

Fox, M. D. & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat.Rev.Neurosci., 8,* 700-711.

Gandotra, S., Paul, S., Daniel, M., Kumar, K., Raj, H., et al., (2004). A preliminary study of rehabilitation needs of in-patients and out-patients with schizophrenia. *Indian Journal of Psychiatry, 46,* 244-255.

Garavan, J., Browne, S., Gervin, M., Lane, A., Larkin, C. et al., (1998). Compliance with neuroleptic medication in outpatients with schizophrenia: relationship to subjective response neuroleptics, attitudes to medication and insight. *Comprehensive Psychiatry, 39,* 215-219.

Kenny, E. R., O'Brien, J. T., Cousins, D. A., Richardson, J., Thomas, A. J., Firbank, M. J., & Blamire, A. M. (2010). Functional connectivity in late-life depression using resting-state functional magnetic resonance imaging. *The American journal of geriatric psychiatry official journal of the American Association for Geriatric Psychiatry*, *18*, 643-651.

Kim, D. I., Mathalon, D. H., Ford, J. M., Mannell, M., Turner, J. A., Brown, G. G. et al. (2009). Auditory oddball deficits in schizophrenia: an independent component analysis of the fMRI multisite function BIRN study. *Schizophr.Bull., 35,* 67-81.

Koshino, H., Carpenter, P.A., Minshew, N.J., Cherkassky, V.L.. Keller, T.A., et al., (2005). Functional connectivity in an fMRI working memory task in high-functioning autism. *Neuroimage, 24,* 810-821.

Leotti, L. A. & Wager, T. D. (2010). Motivational influences on response inhibition measures. *J.Exp.Psychol.Hum.Percept.Perform., 36,* 430-447.

Li, C. S., Yan, P., Sinha, R., & Lee, T. W. (2008). Subcortical processes of motor response inhibition during a stop signal task. *NeuroImage, 41,* 1352-1363.

Liang, M., Zhou, Y., Jiang, T., Liu, Z., Tian, L., Liu, H. et al. (2006).Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. *NeuroReport, 17,* 209-213.

Liddle, P. F., Kiehl, K. A., & Smith, A. M. (2001).Event-related fMRI study of response inhibition. *Human Brain Mapping, 12,* 100-109.

Logan, G.D., Cowan, W.B., Davis, K.A. (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform, 2,* 276-91.

Logan, G. D. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In D. Dagenbach & T. H. Carr (Eds.), *Inhibitory processes in attention, memory, and language* (pp. 675-691). San Diego, CA: Academic Press.

Meda, S.A., Calhoun, V.D., Astur, R.S., Turner, B.M., Ruopp, K., Pearlson, G.D., (2009). Alcohol dose effects on brain circuits during simulated driving: an fMRI study. Hum Brain Mapp.,30, 1257–1270.

Miller, P., Lawrie, S. M., Hodges, A., et.Al., (2001). Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Social Psychiatry and Psychiatric Epidemiology, 36*, 338–342.

Mohr, B., Pulvermuller, F., Cohen, R., Rockstroh, B., (2000). Interhemispheric cooperation during word processing: evidence for callosal transfer dysfunction in schizophrenic patients. *Schizophrenia Research, 46*, 231-239.

Mostofsky, S. H., Schafer, J. G., Abrams, M. T., Goldberg, M. C., Flower, A. A., Boyce, A. et al. (2003). fMRI evidence that the neural basis of response inhibition is task-dependent. *Brain Res.Cogn Brain Res., 17,* 419-430.

Ongur, D., Lundy, M., Greenhouse, J., Shinn, A.K., Menon, V et al., (2010). Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Research, 183,* 59-68.

Perlick, D., Stastny, P., Mattis, S., and Teresi, J. (1992).Contribution of family, cognitive, and clinical dimensions to long term outcome in schizophrenia. *Schizophrenia Research,*6, 257-265.

Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., & Mechelli, A. (2011). Dysconnectivity in schizophrenia: where are we now? *Neuroscience & Biobehavioral Reviews*, *35*, 1110-1124.

Rosenfeld, B., Turkheimer, E., Gardner, W., (1992). Decision Making in a Schizophrenic Population. *Law and Human Behavior*, *16,* 651-662.

Rotarska-Jagiela, A., van de Ven, V., Oertel-Knöchel, V., Uhlhaas, P.J., Vogeley, K., Linden, D.E. (2010). Resting-state functional network correlates of psychotic symptoms in schizophrenia. *Schizophrenia Research, 1,* 21-30.

Ruscher, S. M., De Wit, R. & Mazmanian, D. *(*1997*).*Psychiatric patients' attitudes about medication and factors affecting noncompliance. *Psychiatric Services*, *48*, *82*-85.

Stam,C.J., Jones, B.F., Manshanden, I., van Cappellen, A.M., Montez, T., Verbunt, P.A., et al., (2006). Magnetoencephalographic evaluation of resting-state functional connectivity in Alzheimer's disease*. Neuroimage*, *32*, 1335-44*.*

Stoffers, D., Bosboom, J.L., Deijen, J.B., Wolters, E.C., Stam, C.J., Berendse, H.W., (2008). Increased cortico-cortical functional connectivity in early-stage Parkinson's disease: an MEG study. *Neuroimage, 41,* 212-222.

Sundaram, S.K., Kumar, A., Makki, M.I., Behen, M.E., Chugani, H.T., et al., (2008).Diffusion tensor imaging offrontal lobe in autism spectrum disorder. *Cerebral Cortex, 18,* 2659–2665.

Tu, P., Buckner, R.L., Zollei, L., Dyckman, K.A. et al., (2010).Reduced functional connectivity in a right-hemisphere network for volitional ocular motor control in schizophrenia. *Brain, 133,* 625–637.

Welchew, D., Ashwin, C., Berkouk, K., Salvador, R., Suckling, J., Baron-Cohen, S., Bullmore, E., (2005).Functional disconnectivity of the medial temporal lobe in Aspergers syndrome.*Biological Psychiatry, 57,* 991–998.

Whitfield-Gabrieli, S., Thermenos, H. W., Milanovic, S., Tsuang, M. T., Faraone, S. V., McCarley, R. W. et al. (2009). Hyperactivity and hyperconnectivity of

the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc.Natl.Acad.Sci.U.S.A, 106,* 1279-1284.

Wilcox, C.E., Teshiba, T.M., Merideth, F., Ling, J., Mayer, A.R. (2011). Enhanced cue reactivity and fronto-striatal functional connectivity in cocaine use disorders. *Drug Alcohol Dependence, 115,* 137-144.

Wolf, R.C., Vasic, N., Sambataro, F., Hose, A., Frasch, K., et al., (2009). Temporally anticorrelated brain networks during working memory performance reveal aberrant prefrontal and hippocampal connectivity in patients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry, 8,* 1464-73.

Woodward, N. D., Rogers, B., & Heckers, S. (2011). Functional resting-state networks are differentially affected in schizophrenia. *Schizophrenia Research*, *130*, 86-93.

Yung, A. R., Phillips, L. J., Yuen, H. P., et al (2004) Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophrenia Research, 67,* 131–142.

Zhang, J., Wang, J., Wu, Q., Kuang, W., Huang, X., et al., (2011). Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. *Biol Psychiatry, 15,* 334-42.

Zhou, Y., Liang, M., Jiang, T., Tian, L., Liu, Y., Liu, Z. et al. (2007).Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI.*Neurosci.Lett., 417,* 297-302.