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ASSESSMENT OF ANTIPSYCHOTIC MEDICATION EFFECTS ON DYNAMIC FUNCTIONAL NETWORK CONNECTIVITY IN PATIENTS WITH SCHIZOPHRENIA

by

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A THESIS

Submitted to the graduate faculty of The University of Alabama at Birmingham,
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ASSESSMENT OF ANTIPSYCHOTIC MEDICATION EFFECTS ON DYNAMIC FUNCTIONAL NETWORK CONNECTIVITY IN PATIENTS WITH SCHIZOPHRENIA

KRISTIN K. LOTTMAN

BIOMEDICAL ENGINEERING

ABSTRACT

Schizophrenia, a psychiatric disorder affecting approximately 1% of the population, is often characterized as a disorder of dysconnectivity. Evaluation of the dysconnectivity hypothesis of schizophrenia has been extensively examined via functional neuroimaging studies in order to enhance insight into the disorder's pathology. In particular, resting-state functional connectivity analyses have reported widespread aberrant network connectivity between brain regions in patients; however, consistencies in the directionality of abnormalities are often variable across studies. Recent investigations have begun to analyze functional connectivity dynamically as it is likely these inconsistencies may be a result of the static nature of traditional connectivity measures. In this study, we assess dynamic functional network connectivity in patients with schizophrenia and matched healthy controls through implementation of group independent component and sliding window analyses. Patients completed a resting-state functional magnetic resonance imaging scan while unmedicated and after six weeks of treatment. Data were preprocessed and decomposed into independent components via group independent component analysis and identified as resting-state networks. Sliding window analysis was subsequently performed on post-processed time courses with

variable tapered window sizes (30s, 40s, 44s, 50s, and 60s) and resultant windowed correlation matrices were clustered into discrete connectivity states. Results demonstrated widespread aberrant (increased and decreased) connectivity differences in unmedicated patients across window sizes; however, the vast majority of connectivity differences were most prominent within a single state at small window sizes. Exploratory analyses of connectivity state statistics indicate that unmedicated patients tend to spend less time in states typified by sparse connectivity. Additionally, results found patients tended to dwell longer in smaller windowed states typified by patient hypo-connectivity. Ultimately, our results demonstrate the importance of implementing dynamic analyses to gain connectivity details not obtainable with traditional connectivity analyses. In addition, implementation of these analyses not only improves insight into the role of network dysconnectivity in schizophrenia, but also provides a promising indication of progress towards biomarker identification.

Keywords: schizophrenia, functional connectivity, dynamics, sliding window, fMRI, risperidone

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LIST OF ABBREVIATIONS

AUD	auditory
BOLD	blood oxygenation level dependent
BPRS	Brief Psychiatric Rating Scale
CC	cognitive control
CB	cerebellar
DARTEL	diffeomorphic anatomical registration using exponentiated lie algebra algorithm
DIGS	Diagnostic Interview for Genetic Studies
dFNC	dynamic functional network connectivity
DM	default-mode
EPI	echo-planar imaging
fALFF	fractional amplitude of low frequency fluctuations
fMRI	functional magnetic resonance imaging
FWHM	full width at half maximum
GICA	group independent component analysis
GIFT	Group ICA of fMRI Toolbox
HC	healthy control
HZ	hertz
IC	independent component
ICA	independent component analysis

ICN	intrinsic connectivity network
I_q	quality index
mm	millimeters
MNI	Montreal Neurological Institute
MPRAGE	magnetization prepared rapid acquisition gradient echo
MRI	magnetic resonance imaging
ms	milliseconds
PCA	principal components analysis
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
rsfMRI	resting-state functional magnetic resonance imaging
RSN	resting-state network
s	seconds
SC	sub-cortical
SES	socioeconomic status
sFNC	stationary functional network connectivity
SM	somatomotor
SZ	schizophrenia
TE	echo time
TI	inversion time
TR	repetition time
UAB	University of Alabama at Birmingham
U	unknown
VIS	visual

INTRODUCTION

Schizophrenia

Schizophrenia is a psychiatric disorder that affects approximately 1% of the population (Freedman, 2003; Tandon et al., 2008b). Symptoms of the illness often begin to emerge in individuals between late adolescence and early adulthood. Characteristic symptoms consist of positive symptoms distinguished by hallucinations, delusions, or thought disorders; negative symptoms typified by social withdrawal, flat affect, or anhedonia; and cognitive symptoms such as poor executive functioning, memory deficits, and attention deficits (American Psychiatric Association, 2013; Tandon et al., 2009).

Furthermore, schizophrenia is often described as a heterogeneous disorder since manifestation of characteristic symptoms not only varies across individuals but also in severity. While identification of various risk factors and risk levels for the disorder such as family history (Gottesman et al., 1987; Kendler et al., 1993; Sullivan et al., 2003; Tandon et al., 2008a), urbanicity (Pedersen and Mortensen, 2001; Tandon et al., 2008a), migration (Cantor-Graae and Selten, 2005; Tandon et al., 2008a), and cannabis use (Semple et al., 2005; Tandon et al., 2008a) have increased understanding of the disorder's causation, the exact etiology of schizophrenia still remains unknown (Tandon et al., 2008a). It is believed that these characteristic symptoms of the disorder are an expression of aberrant communication between brain regions rather than discrete brain region abnormalities (Fornito et al., 2012; Friston and Frith, 1995; Stephan et al., 2009).

Currently, schizophrenia is treated with antipsychotic medications that act as antagonists on the D2 dopamine receptors. However, only positive symptoms are mitigated with little effect on negative and cognitive symptoms. Additionally, response to antipsychotic medications is variable among patients, as approximately one-third of patients will not improve with medication (Lieberman et al., 2005) and many will respond poorly to medications (Harrow et al., 1997). Consequently, there is a need for advancement towards a more targeted and effective drug treatment in order to improve long-term prognosis. It is believed that progress towards identification of imaging biomarkers that characterize connectivity abnormalities is necessary for development of more targeted drug treatment and could potentially be facilitated through utilization of the neuroimaging techniques that are the focus of this thesis.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) using blood oxygenation level dependent (BOLD) contrast is a non-invasive neuroimaging technique commonly used to examine brain function. BOLD contrast fMRI examines brain function through an indirect measure of neuronal activity that is based on blood flow and its magnetic properties (Huettel et al., 2008; Logothetis et al., 2001; Ogawa et al., 1990).

The magnetic properties of blood vary based on whether or not the hemoglobin protein molecule is oxygenated or deoxygenated (Huettel et al., 2008). Oxygenated hemoglobin is diamagnetic and has little effect on the surrounding magnetic field due to its lack of unpaired electrons and magnetic moment (Huettel et al., 2008; Ogawa et al., 1990; Pauling and Coryell, 1936). In comparison, deoxygenated hemoglobin is paramagnetic and has greater magnetic susceptibility effects than oxygenated hemoglobin

due to the presence of unpaired electrons and a magnetic moment (Huettel et al., 2008; Ogawa et al., 1990; Pauling and Coryell, 1936). When neurons generate action potentials, blood flow to that brain region increases resulting in a supply of oxygenated hemoglobin greater than can be consumed (Fox et al., 1988; Huettel et al., 2008). Therefore, a change in oxygenated blood concentration induces a change in the magnetic resonance signal detected, also known as BOLD contrast (Huettel et al., 2008; Ogawa et al., 1990). It is important to note that the magnetic susceptibility effects of deoxygenated hemoglobin are also dependent on field strength. Hence, an increase in field strength results in the detection of greater changes in BOLD signal (Gur and Gur, 2010).

Traditionally, fMRI images are acquired while specific task stimuli are presented to and carried out by an individual in the scanner also known as task-based fMRI. However, resting-state fMRI (rsfMRI) measures the spontaneous low-frequency BOLD fluctuations in the brain when no specific task stimuli are presented (Biswal et al., 1995; Cordes et al., 2001; Cordes et al., 2000; Fox and Raichle, 2007). It has been shown that these spontaneous fluctuations can be attributed to the intrinsic or baseline neuronal activity of the brain that corresponds to temporally coherent functional brain networks (Biswal et al., 1995; Damoiseaux et al., 2006; Fox and Raichle, 2007). Although the absence of a task is beneficial when working with a patient population that may have difficulty learning and/or performing a task in the scanner (Fox and Raichle, 2007; Zhou et al., 2010), the presence of non-neuronal noise such as cardiac and respiratory fluctuations (Birn et al., 2006; Fox and Raichle, 2007; Glover et al., 2000; Lund et al., 2006; Wise et al., 2004) in the BOLD signal is a major concern in rsfMRI analysis and must be mitigated prior to implementation of connectivity analyses.

Functional Connectivity

Schizophrenia is described as a disorder of brain connectivity exemplified by uncharacteristic interactions between brain regions, which are likely influenced by abnormal neuronal and physiological processes (Bassett et al., 2012; Friston and Frith, 1995; Stephan et al., 2009; Valli et al., 2011). These uncharacteristic brain interactions are commonly examined via functional connectivity measures.

Functional connectivity is defined as the measure of temporal correlations between spatially separate regions of the brain (Biswal et al., 1995; Fox and Raichle, 2007). More specifically, functional connectivity analyses of rsfMRI examine interactions between intrinsic connectivity networks (ICNs) or resting-state networks (RSNs) as these networks are a representation of the intrinsic or baseline activity of the brain while at rest (Beckmann et al., 2005; Damoiseaux et al., 2006; Fox and Raichle, 2007; Hutchison et al., 2013a; Power et al., 2011; Yeo et al., 2011). Two of the most common methods of examining functional connectivity of RSNs from BOLD data are (1) seed-based analysis and (2) independent component analysis (ICA).

Seed-based analysis is a hypothesis-driven technique in which the BOLD time course from a seed region or region of interest is extracted and temporal correlations or functional connections to all other voxels within the brain are determined (Biswal et al., 1995; Fox and Greicius, 2010; Fox and Raichle, 2007; Joel et al., 2011). However, one major limitation of seed-based analysis is the fact that seed regions must be predefined based on *a priori* hypotheses. In comparison, the data-driven ICA is a blind source signal separation technique in which a mathematical algorithm is utilized to decompose the entire BOLD signal into maximally independent components (Beckmann et al., 2005;

Fox and Greicius, 2010; Fox and Raichle, 2007; Joel et al., 2011; McKeown et al., 1998). These extracted independent component time courses are subsequently utilized to determine within and between network connectivity (Joel et al., 2011). Therefore, the data-driven nature of ICA analysis makes it advantageous to a hypothesis-driven seed-based analysis.

Functional Connectivity in Schizophrenia

Previous studies have shown that rsfMRI functional connectivity is altered in patients with schizophrenia [see (Yu et al., 2012) for review]. These altered functional connectivity patterns in patients with schizophrenia have been shown to be affected by antipsychotic medication treatment (Davis et al., 2005; Hadley et al., 2014; Honey et al., 2003; Lui et al., 2010; Lynall et al., 2010). However, the directionality of these altered functional connections has varied across studies, which ultimately raises questions about how the "static" assumptions made in functional connectivity analysis are directly affecting the reliability of results (Allen et al., 2014; Damaraju et al., 2014; Fox and Greicius, 2010).

Dynamics of Functional Connectivity

While most rsfMRI analyses include at least four to five minutes of data based on previous studies demonstrating that RSN functional connectivity correlation values stabilize with this amount of time (Hutchison et al., 2013a; Van Dijk et al., 2010), recent studies suggest at least nine to thirteen minutes of data greatly enhance the reliability of functional connectivity values (Birn et al., 2013). Ultimately, this illustrates that regional interactions within the brain do not remain constant over time unless examined in long time-scales (Allen et al., 2014; Handwerker et al., 2012; Hutchison et al., 2013a; Jones et

al., 2012; Kiviniemi et al., 2011; Sakoglu et al., 2010). Rather, the dynamic nature of brain activity is not accounted for in traditional functional connectivity measures, as functional connectivity is estimated as the average temporal correlations between RSNs over the length of a scan (Biswal et al., 1995; Fox and Raichle, 2007; Friston, 1994; Lynall et al., 2010). Therefore, traditional functional connectivity measures are based on the major assumption that connections within the brain remain stable over time (i.e., length of rsfMRI scan). The problem in making this assumption may be manifested in the inconsistent functional connectivity pattern differences reported across studies (Calhoun et al., 2009; Damaraju et al., 2014; Fornito et al., 2012; Fox and Greicius, 2010), and ultimately the inability to clinically translate the results.

In comparison, potential fluctuations in functional connectivity interactions over time can be taken into account via time course sampling and subsequent functional connectivity estimation, also known as dynamic functional network connectivity measures. The most common approach to estimating dynamic functional network connectivity is with a sliding window technique (Allen et al., 2014; Handwerker et al., 2012; Hutchison et al., 2013a; Hutchison et al., 2013b; Jones et al., 2012; Kiviniemi et al., 2011; Sakoglu et al., 2010), in which windows of the BOLD time courses are sampled in order to estimate reproducible, transient patterns of functional connectivity ("connectivity states") (Allen et al., 2014; Hutchison et al., 2013a). These connectivity states are believed to be representative of discrete mental states of connectivity that subjects pass through during the scan (Calhoun et al., 2014; Hudson et al., 2014; Hutchison et al., 2013a), an observation not obtainable from traditional functional connectivity measures. Therefore, the nature of dynamic functional network connectivity

analysis avoids the issue of oversimplification of the functional connections of spontaneous fluctuations encountered in traditional functional connectivity measures. The recent emergence and utilization of dynamic functional network connectivity analyses provides promise in progress toward identification of imaging biomarkers characteristic of pathophysiological states such as schizophrenia. In addition, these analyses not only provide greater insight into the role of networks in the healthy human brain, but also into network abnormalities characteristic of mental disorders.

Thesis Format

In this prospective study, a longitudinal rsfMRI experimental design was implemented in order to examine dynamic functional network connectivity in unmedicated patients, as well as to study the effects of the second-generation antipsychotic medication, risperidone. Connectivity states, a representation of transient patterns of functional connectivity, were computed between RSNs identified via group independent component analyses and compared between a group of healthy controls and patients with schizophrenia. The effects of antipsychotic medication were examined with a comparison of connectivity state functional connections in patients with schizophrenia while acutely psychotic, before beginning antipsychotic medication, and after six weeks of treatment. Furthermore, differences in connectivity state dwell times and transition patterns were examined with various statistical analyses.

This thesis is composed of an introduction, a manuscript submitted to *NeuroImage: Clinical* that explores dynamic functional network connectivity in patients with schizophrenia, and a conclusion.

CONNECTIVITY STATE ABNORMALITIES EXHIBITED IN UNMEDICATED PATIENTS WITH SCHIZOPHRENIA USING DYNAMIC FUNCTIONAL NETWORK CONNECTIVITY ANALYSIS AND EFFECT OF ANTIPSYCHOTIC MEDICATION

by

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Submitted to *NeuroImage: Clinical*

Format adapted for thesis

Abstract

The dysconnectivity hypothesis of schizophrenia has been extensively examined via functional neuroimaging studies in order to enhance insight into the neuropathology of the disorder. Resting-state functional connectivity analyses have reported widespread aberrant network integration; however, these abnormalities are variable across studies. Recent investigations have begun to analyze functional connectivity dynamically as it is thought that inconsistencies across studies may be a result of the static nature of traditional functional connectivity measures. In this study, we assess dynamic functional network connectivity in patients with schizophrenia (n=34) and matched (age, gender, smoking status, socio-economic status) healthy controls (n=35) through the implementation of group independent component analysis and sliding window analysis. Patients with schizophrenia completed a 5-minute (150-volume) resting-state functional magnetic resonance imaging scan while unmedicated and after six weeks of antipsychotic medication (risperidone) treatment. Data were preprocessed and decomposed into 100 independent components via group independent component analysis and 42 were identified as resting-state networks – as opposed to artifact. Sliding window analysis was subsequently performed on post-processed time courses with different window sizes (30s, 40s, 44s, 50s, and 60s) and resultant windowed correlation matrices were then clustered into 4 discrete connectivity states. Results demonstrate widespread aberrant connectivity differences in patients with schizophrenia across window sizes; however, the vast majority of connectivity differences were most prominent within a single state at small window sizes. More specifically, vast subcortical, visual, and cerebellar connectivity abnormalities were manifested at window sizes of 30s, 40s, and 44s in a state typified by

strong within visual network connectivity. Exploratory analyses of connectivity state statistics indicate that unmedicated patients tend to spend significantly less time in states typified by sparse connectivity; however, antipsychotic medication treatment appears to reduce differences between controls and patients. Additionally, a positive correlation was found between baseline patient dynamic connectivity and subsequent treatment response in subcortical and cognitive control networks. Ultimately, our results demonstrate the importance of implementing dynamic analyses in order to further comprehend the dysconnectivity hypothesis of schizophrenia, as well as provide a promising indication of progress towards biomarker identification in patients with schizophrenia.

Keywords: functional connectivity, dynamics, resting state, schizophrenia, risperidone, independent component analysis

1. Introduction

Schizophrenia is often described as a disorder of brain connectivity characterized by abnormal network integration between cortical areas, and likely related to clinical symptoms (Bassett et al., 2012; Friston and Frith, 1995; Stephan et al., 2009; Valli et al., 2011). Structural and functional dysconnectivity in schizophrenia has been extensively proposed in neuroimaging studies. A common approach to characterizing functional dysconnectivity is through evaluation of functional connectivity – the measure of temporal coherence of low frequency blood oxygenation level dependent (BOLD) signal fluctuations between spatially separate regions of the brain (Biswal et al., 1995; Fox and Raichle, 2007; Friston and Frith, 1995). More specifically, analyses of resting-state functional magnetic resonance imaging (fMRI) data has allowed for characterization of intrinsic network connectivity aberrations (Beckmann et al., 2005; Damoiseaux et al., 2006; Fox and Raichle, 2007; Hutchison et al., 2013a; Jafri et al., 2008; Power et al., 2011; Sorg et al., 2007; Yeo et al., 2011).

Traditionally, functional connectivity is evaluated over long time scales, or the length of the scan. However, this "static" approach to connectivity analysis disregards the dynamic nature of brain activity by assuming constant connectivity patterns over time (Calhoun et al., 2014; Hutchison et al., 2013a). Recent reports attribute functional connectivity inconsistencies across studies to the oversimplification of data in traditionally static functional connectivity analyses (Calhoun et al., 2009; Damaraju et al., 2014; Fornito et al., 2012; Fox and Greicius, 2010; Hutchison et al., 2013a; Rashid et al., 2014). The recent emergence of dynamic functional connectivity analysis aims to address this data averaging issue by calculating transient patterns of functional connectivity

through windowed time course sampling (Allen et al., 2014; Damaraju et al., 2014; Handwerker et al., 2012; Hutchison et al., 2013a; Hutchison et al., 2013b; Jones et al., 2012; Kiviniemi et al., 2011; Sakoglu et al., 2010). However, the obstacle of determining the correct window size for sliding window analysis still remains. While some studies have indicated a window size between 30 and 60 seconds robustly estimates functional connectivity (Allen et al., 2014; Shirer et al., 2012), others have explored window sizes ranging from 30 seconds to 240 seconds (Allen et al., 2014; Damaraju et al., 2014; Handwerker et al., 2012; Hutchison et al., 2013a; Hutchison et al., 2013b; Leonardi and Van De Ville, 2015; Sakoglu et al., 2010). In this work, we aim to address this issue through utilization of five window sizes between 30 and 60 seconds to evaluate dynamic functional connectivity.

Furthermore, clustering of the transient patterns of connectivity results in connectivity states that are believed to be representative of discrete mental states of connectivity that subjects pass through during the scan (Allen et al., 2012; Calhoun et al., 2014; Hudson et al., 2014; Hutchison et al., 2013a). In capturing the fluctuations in network interactions over time, and ultimately more descriptively characterizing network integration, the progress towards identifying imaging biomarkers is enhanced.

The purpose of this study was to evaluate the dynamic nature of functional network connectivity in unmedicated patients with schizophrenia and the effects of antipsychotic medication. To our knowledge, the effects of antipsychotic medication on dynamic functional network connectivity have not been observed in patients with schizophrenia. Resting-state fMRI scans were obtained for patients while unmedicated, as well as after six weeks of risperidone treatment. We hypothesize that unmedicated

patients with schizophrenia will exhibit significant connectivity abnormalities compared to healthy controls. We predict these connectivity abnormalities will be variable across networks but will be state-specific rather than manifesting in all connectivity states.

2. Methods

2.1 Participants

Thirty-four unmedicated patients with schizophrenia were recruited from the emergency room, inpatient units, and various outpatient clinics at the University of Alabama at Birmingham (UAB). Additionally, 35 matched healthy controls based on age, gender, smoking status, and socio-economic status were recruited using flyers and advertisements in the university newspaper. This study was approved by the UAB Institutional Review Board, and written informed consent for participation was obtained after participants were found competent to provide informed consent (Carpenter et al., 2000).

Diagnoses were established with review of patient medical records and evaluation by two board certified psychiatrists, and confirmed using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994). Patients included in the study had been off antipsychotic medication for at least 10 days; we did not stop medication to meet this criterion. Exclusion criteria were major medical conditions, neurological disorders, history of head trauma with loss of consciousness, substance abuse within 6 months of imaging (with the exception of nicotine), use of medication affecting brain function, pregnancy, and MRI contraindications. Healthy control exclusion criteria also included a history of Axis I disorders personally or in first-degree relatives.

Subjects who were either medication naïve or had been off antipsychotic medications were enrolled in a six-week trial with risperidone using a flexible dosing regimen. Medication was managed by two psychiatrists (ACL and NVK), and dose determinations were based on therapeutic and side effects. Starting doses were 1-3 milligrams; titration was done in 1-2 milligram increments. Compliance was monitored by pill counts at each visit. Concomitant antidepressant or mood stabilizing medication was allowed to be used as indicated.

2.2 Study Design

Participants completed a resting-state fMRI scan of at least 5 minutes (150 volumes) in length. For data length consistency across participants, additional volumes over 5 minutes were discarded (Allen et al., 2014). All participants were scanned at baseline. Patients were then scanned after six weeks of treatment to allow adequate time for clinical response (Hadley et al., 2014; Marder et al., 2002). Of the 34 patients with schizophrenia enrolled, six subjects dropped out of the study prior to the second scan. One subject was excluded from baseline analysis due to an insufficient number of scan volumes. In addition, no resting state scans were obtained for four subjects at week 6, leaving data for 33 patients at baseline and 24 patients at week 6 in the final analysis. Additionally, 19 of the 35 recruited healthy controls were scanned for a second time six weeks after the baseline scan. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was used to assess symptom severity weekly. Cognitive function was assessed for both groups at baseline using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998).

2.3 Scanning Parameters

All scans were performed with a 3 Tesla head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany), with a circularly polarized transmit/receive head coil. High-resolution structural scans were acquired for anatomical reference using the 3-dimensional T1-weighted magnetization-prepared rapid acquisition gradient-echo sequence (repetition time/echo time/inversion time [TR/TE/TI]= 2300/3.93/1100ms, flip angle= 12°, 256 × 256 matrix, 1-mm isotropic voxels). Resting-state fMRI scans were acquired using a gradient recalled echo-planar imaging sequence (TR/TE= 2000/30ms, flip angle= 70°, field of view= 192 × 192mm^2, 64 × 64 matrix, 6mm slice thickness, 1mm gap, 30 axial slices). Participants were instructed to keep eyes open and stare passively ahead during the scan.

2.4 Preprocessing

Data preprocessing was performed with SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). Resting-state fMRI data were slice-timing corrected, realigned, normalized to Montreal Neurological Institute (MNI) space with the diffeomorphic anatomical registration using exponentiated lie algebra algorithm (DARTEL) (Ashburner, 2007), resampled to 1.5 mm^3, and smoothed with a Gaussian kernel to 6 mm full width at half maximum. Prior to group independent component analysis, data were variance normalized to facilitate decomposition of subcortical and cortical networks (Damaraju et al., 2014).

2.5 Group Independent Component Analysis

Group-level spatial independent component analysis was performed via the Group ICA of fMRI Toolbox (GIFT, http://mialab.mrn.org/software/gift). Subject specific principal component analysis (PCA) was implemented in the GIFT toolbox by reducing

the data to 120 principal components, which were subsequently decomposed into 100 components via group data reduction (Allen et al., 2014). The expectation maximization algorithm was used to carry out PCA in a memory efficient manner (Allen et al., 2014; Roweis, 1998). The Infomax algorithm (Allen et al., 2014; Bell and Sejnowski, 1995) was then applied to the PCA reduced data to generate 100 spatially independent components. Component stability/quality was measured by repeating the Infomax algorithm 20 times in ICASSO (http://www.cis.hut.fi/projects/ica/icasso) (Allen et al., 2014; Damaraju et al., 2014). Subject-specific spatial maps and time courses were generated via GICA back-reconstruction (Erhardt et al., 2011). Following back-reconstruction, subject spatial maps and time courses were scaled to z-scores.

2.6 Postprocessing

Three reviewers (KKL, NVK, DMW) classified independent components as resting state networks (RSNs) – as opposed to artifact – based on visual inspection of group-level component spatial maps and evaluation of power spectra data. Group-level component spatial maps were inspected and classified as RSNs with expectations that peak activation clusters occur primarily in gray matter, correspond anatomically to brain networks, and meet the RSN expectations presented in previous studies (Allen et al., 2014; Allen et al., 2011; Damaraju et al., 2014). To facilitate component classification as RSNs, component power spectra data were evaluated using the fractional amplitude of low frequency fluctuations (fALFF) (Allen et al., 2011; Zou et al., 2008) in order to validate component time courses were characterized by predominantly low-frequency fluctuations (Allen et al., 2014; Cordes et al., 2001; Cordes et al., 2000). The three reviewers identified 42 RSNs from the 100 extracted components, as illustrated in Figure

1A. RSNs were labeled based on results from brain atlas toolboxes utilized in SPM8 – xjView (http://www.alivelearn.net/xjview8/) and WFU_PickAtlas (http://www.nitrc.org/projects/wfu_pickatlas/). Additionally, RSN labels were determined based on correspondence to the 50 components presented in (Allen et al., 2014), as well as label consensus among all three reviewers (See Table S1 for RSN peak activations). Labeled RSNs were then organized into seven different networks including subcortical, auditory, somatomotor, visual, cognitive control, default mode, and cerebellar (Allen et al., 2014). Three components were classified as unknown networks after reviewer inspection of RSNs resulted in no clear distinct label.

Following RSN identification, framewise displacement was regressed from the subject specific RSN time courses. Framewise displacement was computed as the absolute frame-to-frame displacement of the brain from the six realignment parameters using a radius of 50mm to convert angle rotations to displacements (Hadley et al., 2014; Power et al., 2012). Subsequently, subject specific RSN time courses were detrended, despiked, and low-pass filtered (0.15 Hz cutoff) in accordance with previous studies (Allen et al., 2014; Damaraju et al., 2014).

2.7 Static Functional Network Connectivity Analysis

Traditional or static functional network connectivity was estimated for each subject as the pairwise correlation between whole RSN component time courses, resulting in a 42-by-42-component correlation matrix (Figure 1B). After Fisher-Z transformation, variance associated with the covariates of age and gender was removed from correlation values. Corrected correlation matrices for subjects in a group were then averaged together resulting in a group-level connectivity matrix. Subsequently, within

and between group differences in static functional network connectivity matrices were evaluated via univariate t-tests with a significance value of $p<0.05$. Bootstrap resampling (i.e., resampling with replacement) was conducted with a resampling rate of 1000 to determine reliability of significant group differences in connectivity. Group differences ($p<0.05$) that occurred in at least 95% of the 1000 bootstrap resamples were considered significant.

2.8 Dynamic Functional Network Connectivity Analysis

A sliding window technique was used to estimate dynamic functional network connectivity where windowed segments of the component time courses were used to compute transient functional network connectivity patterns (Figure 1C). Sliding window analysis was iteratively performed with window sizes of 30s, 40s, 44s, 50s, and 60s. A Gaussian (σ=3 TRs) window of the respective size was slid through the time course in steps of 1 TR in order to obtain windowed correlation matrices for each subject. Due to potential effects on covariance estimation from sampling short time windows, windowed correlation matrices were generated by estimating the covariance of the L1 regularized inverse covariance matrix, which was carried out utilizing a graphical LASSO framework in the GIFT Toolbox (Allen et al., 2014; Damaraju et al., 2014; Friedman et al., 2008; Smith et al., 2011; Varoquaux et al., 2010).

2.9 Clustering

In order to characterize reoccurring patterns of connectivity across groups and time, k-means clustering was performed on the windowed correlation matrices. Clustering of a sub-sampled number of windows (i.e., windows with relative maxima of variance) for all groups and time points was carried out in order to estimate initial cluster

centroids (cluster medians) (Allen et al., 2014; Damaraju et al., 2014). The sum of absolute differences or L1 distance method was used with a maximum of 150 iterations for k-means cluster computation. The optimal number of cluster states was determined to be four based on evaluation of the elbow criterion of the ratio of within cluster sum of squares distance to between cluster sum of squares distance (Damaraju et al., 2014; Zhao et al., 2009). Resultant centroid states from the clustering of sub-sampled data were subsequently used as initial clustering positions for clustering of all subject and group data. Figure S1 depicts resultant cluster centroids for all subjects and groups at each respective window size.

2.10 Group Differences in Dynamic Functional Network Connectivity

Following k-means clustering of data from all subjects, mean group-level connectivity centroid states were calculated from the group's subject medians of windows assigned to each respective state (Damaraju et al., 2014). Subsequently, univariate t-tests were performed on the age and gender variance-corrected connectivity states to evaluate group differences. Reliability and stability of group differences in connectivity for each state were determined with bootstrap resampling implemented in the same manner as in static functional network connectivity analysis. Group differences (p<0.05) that occurred in at least 95% of the 1000 bootstrap resamples were considered significant. Exploratory post-hoc analyses examining group differences in state statistics such as dwell times (i.e., average amount of time spent occupying a state before switching to another) and overall amount of time spent in a state were implemented using univariate t-tests. Transition matrix differences for each group were also evaluated via chi-square methods (Anderson and Goodman, 1957; Billingsley, 1961; Goodman, 1958).

2.11 Treatment Response

Due to the aforementioned dropout of six subjects, as well as the insufficient number of scan volumes for one subject at baseline, only 27 subjects possessed sufficient data for treatment response analyses. Treatment response was evaluated as the percent change in positive BPRS scores from baseline to week 6. The relationship between baseline functional connectivity (age and gender variance-corrected) and subsequent patient treatment response was examined via univariate tests utilized in the MANCOVAN toolbox (http://mialab.mrn.org/software/mancovan). Univariate tests were carried out for static and dynamic functional connectivity values. Significant effects (p<0.05) that occurred in at least 95% of 10,000 bootstrap resamples were considered significant.

3. Results

3.1 Demographics

Average dose of risperidone was 2.65+/- 1.11mg at the second scan and 4.36+/- 1.45mg at the third scan. Twelve subjects were concomitantly treated with benztropine, two with trazodone, one each was prescribed mirtazapine, amitriptyline, and valproic acid. No significant differences in age, gender, parental socioeconomic status, smoking status, or daily cigarette use were observed between healthy controls and patients. Patients exhibited a decrease in total BPRS scores from 48.29±9.38 at baseline to 36.81±10.84 and 30.57±8.47 after one and six weeks of medication, respectively. In comparison to healthy controls, patients scored significantly lower on RBANS (Table 1).

3.2 Resting State Network Identification

The 42 independent components identified as RSNs are depicted in Figure 1A. Labeled RSNs were then organized into seven different networks including subcortical (3 RSNs), auditory (2 RSNs), visual (9 RSNs), somatomotor (8 RSNs), cognitive control (9 RSNs), default mode (5 RSNs), and cerebellar (3 RSNs; Table S1).

3.3 Group Differences in Static Functional Network Connectivity

Mean static functional network connectivity matrices for healthy controls, unmedicated patients, and week 6 patients are illustrated in Figure 2A-C. In comparison to healthy controls, unmedicated patients demonstrated significantly stronger connections within the visual and cognitive control networks (Figure 2D). Additionally, unmedicated patients exhibited hyper-connectivity between connections in the cognitive control networks and the subcortical and visual networks, as well as between connections in the visual networks and the cerebellar and unknown networks. However, unmedicated patients showed a weaker connection between a cognitive control and subcortical network connection (i.e., middle frontal gyrus (IC 15) to caudate/putamen (IC 34)) in comparison to controls. Moreover, unmedicated patients exhibited hyper-connectivity between a default mode and unknown network connection. In comparison to unmedicated patients, week 6 patients exhibited decreased connectivity in connections within the somatomotor network and between the visual and unknown networks (Figure 2E).

3.4 Group Differences in Dynamic Functional Network Connectivity

Cluster centroids for all subjects and time points at each window size are shown in Figure S1. All centroids illustrate some hyper-connectivity within the visual and somatomotor networks. In particular, state 4 represents a relatively hyper-connected state among all networks. In comparison, state 2 represents the relatively least connected state

among all states with the lowest average correlation value from all connections. Healthy control and unmedicated patient group differences in connectivity state patterns for each window size are illustrated in Figure 3B. A summary of the group differences depicted in Figure 3B is presented in Figure 4. Results indicate that the total number of differences in connectivity decreases as window size increases in state 1 (with the exception of the 60s window). In comparison to controls, unmedicated patients regularly demonstrate hyper-connected group differences among all states in the majority of window sizes, in which states 2, 3, and 4 are predominantly characterized by hyper-connectivity differences. Additionally, aberrant connectivity across the subcortical, visual, and cerebellar networks in patients represents most of the connectivity differences present at the 30s, 40s and 44s windows in state 1. More specifically, patients consistently demonstrate hypo-connectivity between subcortical–visual, subcortical–cerebellar, and cerebellar–visual networks at these window sizes. However, at the 50s and 60s windows, this subcortical and cerebellar network hypo-connectivity is no longer present. Rather, these state 1 windows are characterized by patient hyper-connectivity in visual–visual and visual–cerebellar network components that are also present in the 44s window. Additionally, patient hyper-connectivity in state 1 is consistently exhibited in default mode–unknown network components in the first three windows. Patient hyper-connectivity between a somatomotor and subcortical network connection is exhibited only at small window sizes accompanied by subcortical–visual, subcortical–default mode, and subcortical–cerebellar hypo-connectivity. Examination of state 2 connectivity differences does not result in stable connectivity differences across window sizes with the exception of a subcortical–somatomotor hyper-connection at 40s and 44s in patients. Patient hyper-connectivity in a

visual–visual network component is reliably exhibited in state 3 in window sizes greater than 30s. In state 4, patient hyper-connectivity is exhibited in subcortical–cognitive control, cognitive control–cognitive control, and default mode–unknown network components across 40s, 44s, 50s, and 60s windows.

In addition, evaluation of state connectivity differences across time in patients with schizophrenia indicates widespread connectivity modulations with risperidone treatment. In accordance with significant baseline results and known effects of antipsychotic medication in subcortical regions, longitudinal results will focus primarily on subcortical network abnormalities (longitudinal results are illustrated in their entirety in Figure S2). Specifically, in comparison to unmedicated patients, week 6 patients demonstrated decreased connectivity between only one subcortical network connection (i.e., subcortical–somatomotor) in state 1 at the 40s window. However, subcortical network connectivity alterations were demonstrated primarily in state 2 with week 6 patients – in comparison to unmedicated patients – exhibiting decreased connectivity between subcortical and somatomotor networks at the 40s and 44s windows. Additionally, in contrast to baseline, decreased connectivity in medicated patients was exhibited between subcortical and cognitive control networks at 44s and 50s windows. Moreover, week 6 patients demonstrated increased subcortical connectivity with the default mode network in state 2 and the cerebellar network in state 3 at the 40s window. Examination of differences between healthy control time points indicated only one subcortical network connectivity abnormality present in state 1 between the cognitive control network at the 60s window.

Exploratory post-hoc analyses of group dwell times, overall fraction of time spent in a state, as well as transition probabilities aimed to examine potential driving factors for dynamic functional network connectivity differences between groups. No significant group differences in transition probabilities between states across groups and window sizes were observed. Differences in dwell times and the fraction of time groups occupy individual states are shown in Figure 5. Comparison of the fraction of time groups occupy individual states indicate that unmedicated patients occupy state 2 significantly less and state 3 significantly more than healthy controls ($p<0.05$). In accordance with these results, patient (unmedicated) group mean dwell time in state 2 is significantly less than healthy controls across all windows. Additionally, in comparison to healthy controls, patient fraction of time and mean dwell time in state 2 tends to normalize towards healthy control values with medication treatment at all window sizes. In the 30s, 40s, and 44s windows, patients at baseline and after 6 weeks of medication tend to dwell in state 1 significantly longer than controls. This increased state 1 dwell time at small window sizes corresponds to state 1 window sizes exhibiting greater connectivity differences in baseline patients.

3.5 Effects of Treatment Response

Static functional network connectivity results indicate no correlation between baseline connectivity values and treatment response. However, correlation between baseline connectivity and treatment response is demonstrated in dynamic functional network connectivity (Figure 6). Using a 30s window, treatment response was positively correlated to a subcortical–visual network connection in state 4. No correlations (with the exception of unknown networks) were exhibited at the 40s and 44s windows. At 50s,

state 3 subcortical–cognitive control and cognitive control–cognitive control network connections, as well as state 2 cognitive control–default mode network connections, were positively correlated to treatment response. Additionally, the positive correlation between treatment response and state 3 cognitive control–cognitive control network was also present at the 60s window. However, due to the small number of subjects exhibiting state 4, as well as minimum observation requirements for the regression algorithm, state 4 effects of treatment response at 40s, 44s, 50s, and 60s windows were not obtainable.

4. Discussion

To our knowledge, this is the first dynamic functional network connectivity study examining unmedicated patients with schizophrenia, as well as the effects of antipsychotic medication. We describe connectivity differences, both hyper- and hypo-connectivity, between controls and unmedicated patients in most of the states across the five different window sizes. Exploratory analyses of state statistics indicate that unmedicated patients differ in the time spent in states 2 and 3 in comparison to controls, but this appears to normalize with risperidone. In addition, a positive correlation was found between unmedicated patient dynamic connectivity and subsequent treatment response in subcortical and cognitive control networks in larger window sizes.

In unmedicated patients, our static and dynamic functional network connectivity results reveal altered patterns of functional connectivity within higher order (cognitive control) and sensory (visual) networks as well as between networks (sensory-sensory, sensory-subcortical, sensory-cerebellar, cognitive control-sensory and cognitive control-subcortical). These results are in line with recent studies in medicated patients demonstrating altered systems-level brain network dysfunction that suggest impaired

integration within and between bottom-up and top-down networks (Kaufmann et al., 2015; Liang et al., 2006). In a group of medicated patients, Damaraju and colleagues report extensive connectivity abnormalities between subcortical and sensory networks in connectivity states characterized by sensory network (i.e., auditory, visual, and somatomotor) hyper-connectivity (Damaraju et al., 2014). Like studies that use a seed-based (Anticevic et al., 2014; Woodward et al., 2012) or static and dynamic (Damaraju et al., 2014) functional connectivity approaches in medicated patients, we observe increased subcortical-somatomotor connectivity in unmedicated patients. In addition, these subcortical networks displayed decreased functional connectivity with visual, default mode, and cerebellar networks, which is also in line with prior results in medicated patients (Anticevic et al., 2014; Woodward et al., 2012). Our observations - both static and dynamic - of within and between visual networks functional alterations are consistent with a growing number of studies implicating abnormal visual processing in schizophrenia [see (Javitt and Freedman, 2015) for review]. However, contrary to numerous resting-state studies reporting aberrant default mode network connectivity in patients with schizophrenia [see (Williamson and Allman, 2012) for review], our results – both static and dynamic – indicate no within default mode network connectivity abnormalities. While this incongruity with previous literature may be a result of our enrollment of unmedicated rather than medicated patients, recent reports have demonstrated no significant differences in default mode connectivity in medicated patients (Baker et al., 2014; Wolf et al., 2011).

While our static and dynamic results show, in general, good agreement, the dynamic analysis provided a more fine-grained comparison; state 1 at shorter windows

and state 4 at longer windows were especially informative. While shorter windows captured more frequent patterns of decreased functional connectivity, the longer windows, in line with the static results, showed mostly increased connectivity. These findings are consistent with previous dynamic functional network connectivity analyses in medicated patients illustrating that connectivity pattern characteristics occur in some but not all connectivity states (Calhoun et al., 2014; Damaraju et al., 2014).

While the exact etiology of the connectivity states presented in this work is unknown, recent studies have reported that connectivity states may correspond to stages of consciousness (Calhoun et al., 2014; Hudson et al., 2014). Therefore, these characteristic state-dependent connectivity patterns exhibited in dynamic analysis are promising for future identification of potential imaging biomarkers representative of the disorder of schizophrenia (Calhoun et al., 2014).

Consistent with our prior work (Hadley et al., 2014), we found that some patterns of dynamic functional connectivity at baseline while patients were unmedicated, were predictive of subsequent response to medication. Functional connectivity patterns between subcortical [caudate/putamen (IC50)] and cognitive control networks and within nodes of the cognitive control network were identified as predictive of treatment response. In addition, these patterns were significantly different between unmedicated patients and healthy controls, and demonstrated changes over time with medication. Our findings lend support to the idea that the brain is functionally wired in a way that does or does not favor response to antipsychotic medications. A similar modulation of connectivity between the caudate and the prefrontal cortex as a function of clinical

response, albeit without evidence of baseline dysconnectivity, has been reported by Sarpal et al. using striatal seeds (Sarpal et al., 2015).

In accordance with significant baseline results and known effects of antipsychotic medication in subcortical regions [see (Abi-Dargham and Laruelle, 2005) for review], we limited our investigation of functional changes over time to subcortical networks. In unmedicated patients, subcortical to somatomotor connectivity was increased and this connectivity decreased with treatment. The opposite was observed for the subcortical-default mode and subcortical-cerebellar networks. On the other hand, the subcortical to visual connectivity that showed important differences with healthy controls in unmedicated patients, was not affected by treatment. A short-term evaluation of a group of medication-naïve, first episode schizophrenia patients by Lui and colleagues illustrates the effect of second-generation antipsychotics on normalizing abnormal functional connections in patients with schizophrenia; however, Lui et al. also found that non-aberrant functional connections were also impacted by risperidone treatment demonstrating the non-specific impact of antipsychotic medications on functional connectivity (Lui et al., 2010).

The differences in connectivity, dwell time, and fraction of time patients reside in connectivity states reiterate the advantage of the dynamic approach to examining functional connectivity. Our reported results indicate that examination of functional connectivity differences in a static manner may be an oversimplification.

The work presented in this paper is subject to several limitations. A sliding window analysis was implemented with a window size ranging from 15 to 30 TRs (30-60s) in order to estimate connectivity dynamics. Previous studies have indicated a

window size between 30 and 60 seconds robustly estimates functional connectivity (Allen et al., 2014; Shirer et al., 2012); however, a standard window size has yet to be established. Based on the variability in connectivity differences among small incremental window sizes, future work should focus on developing a data-driven method for optimally determining window size that best fits the data of interest. Similarly, time-frequency approaches may also be useful as such approaches do not require windowing (Yaesoubi et al., 2015a). Additionally, due to the lack of a placebo group in this study, changes in functional connectivity cannot definitively be characterized as medication effects. Although the sample size used in this study is sufficient for robustly estimating static functional connectivity, state connectivity patterns and group differences may be impacted from an inadequate number of subjects exhibiting certain states. Additionally, due to the complex nature of dynamic connectivity patterns (e.g., differences not present in window sizes similar in length), development of multifaceted statistics to capture these complexities would be advantageous. For example, current analyses restrict subjects to exhibiting a single connectivity state at a specific time when there may in fact be an overlap in connectivity state manifestation. The ability to capture potentially overlapping connectivity states (Calhoun et al., 2014; Leonardi et al., 2014; Miller et al., 2014; Yaesoubi et al., 2015b) may provide critical information to ultimately understanding the intricacies of brain function.

Overall, correspondence in static and dynamic results is demonstrated; however, dynamic analysis provides a more comprehensive description of disorder-related abnormalities. Ultimately, this additional information provided by dynamic analyses may be used in the advancement towards identification of imaging biomarkers.

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Table 1: Demographics and clinical assessments[a]

	HC (n=35)	SZ (n=34)	t/χ^2	*p*-value
Age (years)	32.00±8.90	32.38±10.43	-0.164	0.87
Gender (male/female)	25/10	23/11	0.116	0.733
Parental SES[b]	5.80±4.21	7.26±6.39	23.17	0.058
Smoking status (Y/N)	22/13	26/8	1.510	0.219
Smoking (packs per day)	0.61±0.61	0.59±0.53	0.168	0.867
Diagnosis				
Schizophrenia	-	31		
Schizoaffective disorder	-	3		
Illness characteristics				
Illness duration (years)	-	9.59±9.94		
First episode	-	12		
Prior antipsychotic treatment				
Antipsychotic naïve	-	17		
Antipsychotic free interval (months)	-	23.08±44.42		
Baseline BPRS[c] *(n=34)*				
Total score	-	48.29±9.38		
Positive symptom subscale	-	9.53±3.04		
Negative symptom subscale	-	6.79±2.51		
Week 1 BPRS (n=31)				
Total score	-	36.81±10.84		
Positive symptom subscale	-	7.00±3.24		
Negative symptom subscale	-	5.06±2.06		
Week 6 BPRS (n=29)				
Total score	-	30.57±8.47		
Positive symptom subscale	-	4.86±2.38		
Negative symptom subscale	-	5.39±2.42		
RBANS				
Total index	93.74±14.33	70.21±13.76	6.96	<0.001
Immediate memory	95.74±12.73	74.68±16.86	5.87	<0.001
Visuospatial	87.26±19.35	71.41±15.48	3.75	<0.001
Language	100.2±14.04	84.71±12.85	4.78	<0.001
Attention	100.34±19.33	79.03±20.32	4.47	<0.001
Delayed memory	93.06±11.83	72.53±19.10	5.35	<0.001

Abbreviations: HC, healthy control; SZ, schizophrenia; SES, socioeconomic status; Y, yes; N, no; BPRS, Brief Psychiatric Rating Scale; RBANS, Repeated Battery for the Assessment of Neuropsychological Status.

[a]Mean±SD unless otherwise indicated.

[b]SES ranks reported from Diagnostic Interview for Genetic Studies scale (1-18); high rank (lower numerical value) corresponds to high socioeconomic status. Data unavailable for 7 participants (1 HC, 6 SZ).

[c]BPRS reported on 1-7 scale; positive (conceptual disorganization, hallucinatory behavior, and unusual thought content); negative (emotional withdrawal, motor retardation, and blunted affect).

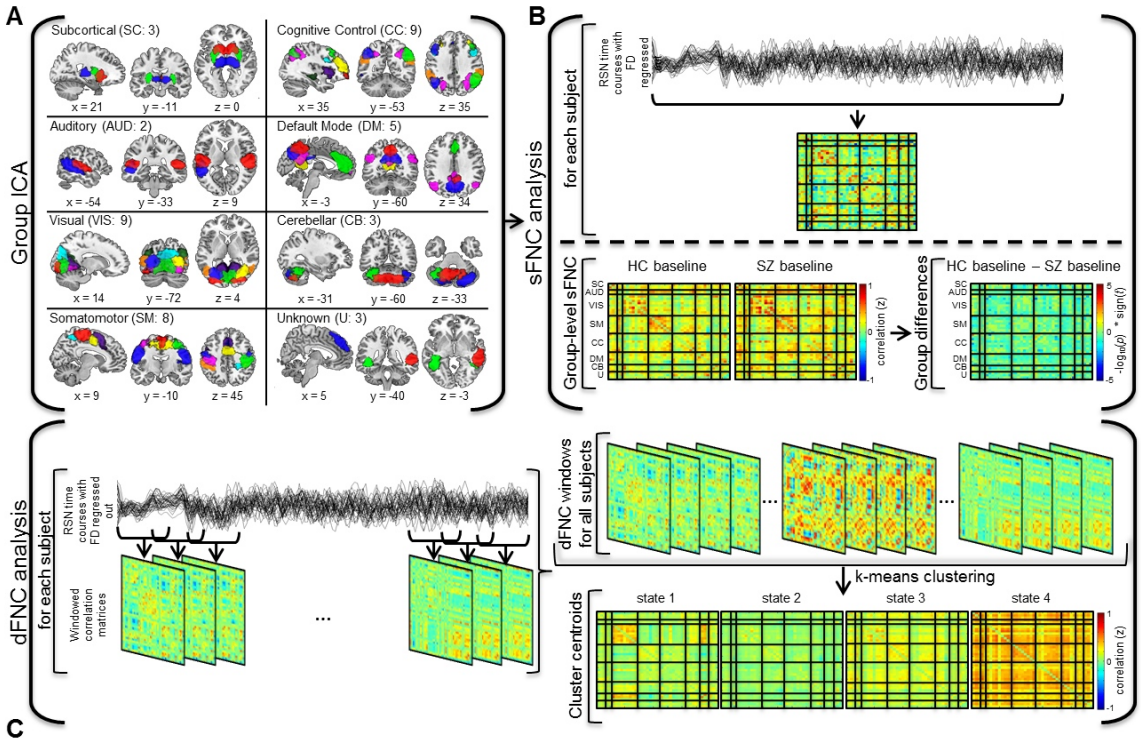

Figure 1: Schematic of functional network connectivity analyses. Analyses involved three major steps: Group independent component analysis (ICA; A), static functional network connectivity (sFNC) analysis (B), and dynamic functional network connectivity (dFNC) analysis (C). (A) RSN composite maps of the 42 RSNs extracted from the data via group ICA and categorized into subcortical (SC), auditory (AUD), visual (VIS), somatomotor (SM), cognitive control (CC), default mode (DM), cerebellar (CB), and unknown (U) networks. Each color in the composite map represents a different component and the number of components grouped in each category is indicated next to the category name. Peak activations of individual components can be seen in Table S1. (B) The entire length of the RSN time courses are used in order to determine the sFNC for each subject and subsequently for each group of subjects. Differences in connectivity are determined between groups – following age and gender correction – via univariate t-tests on bootstrap resampled data. Group differences (p<0.05) that occur in 95% of the 1000 bootstrap resamples are considered significant. (C) In contrast to sFNC analysis, dFNC analysis computes functional network connectivity on windows of the RSN time courses and hence windowed correlation matrices are generated for each subject. Concatenation of dFNC windows for all subjects and subsequent k-means clustering of the windows results in cluster centroids or connectivity states. Significant group differences are determined in the same manner as in sFNC analysis. FD, framewise displacement; HC, healthy control; SZ, schizophrenia.

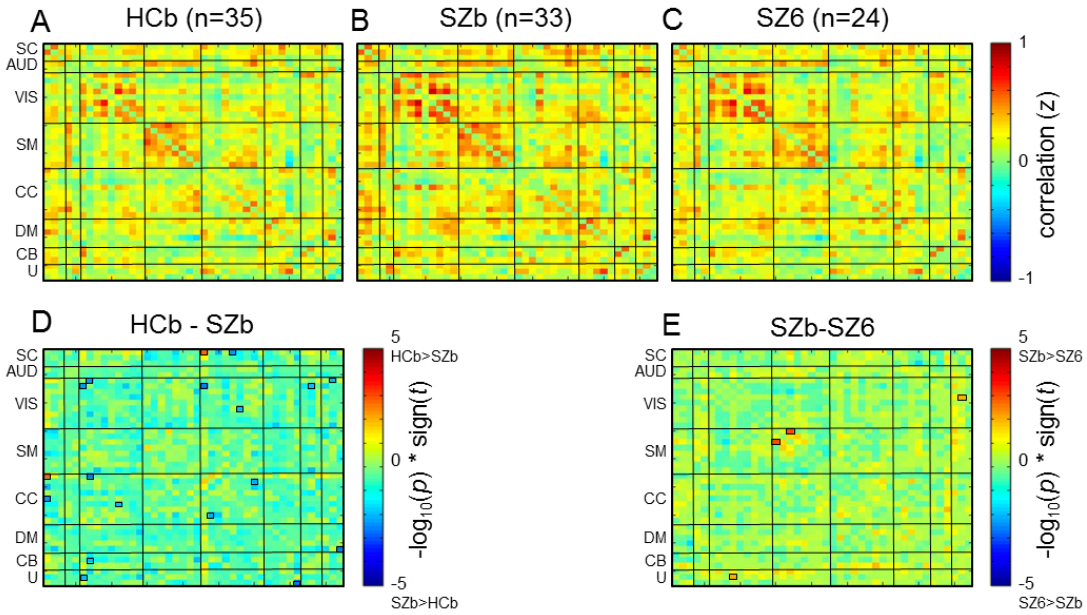

Figure 2: Static functional network connectivity. Group-level mean static functional network connectivity for (A) 35 healthy controls at baseline (HCb), (B) 33 unmedicated patients with schizophrenia (SZb), and (C) 24 patients after 6 weeks of medication (SZ6). Group differences are shown between (D) healthy controls and unmedicated patients (HCb-SZb) and (E) unmedicated patients and week 6 patients (SZb-SZ6). Significant group differences outlined with a small black box are indicated if occurrence is significant ($p<0.05$) in 95% of 1000 bootstrap resamples.

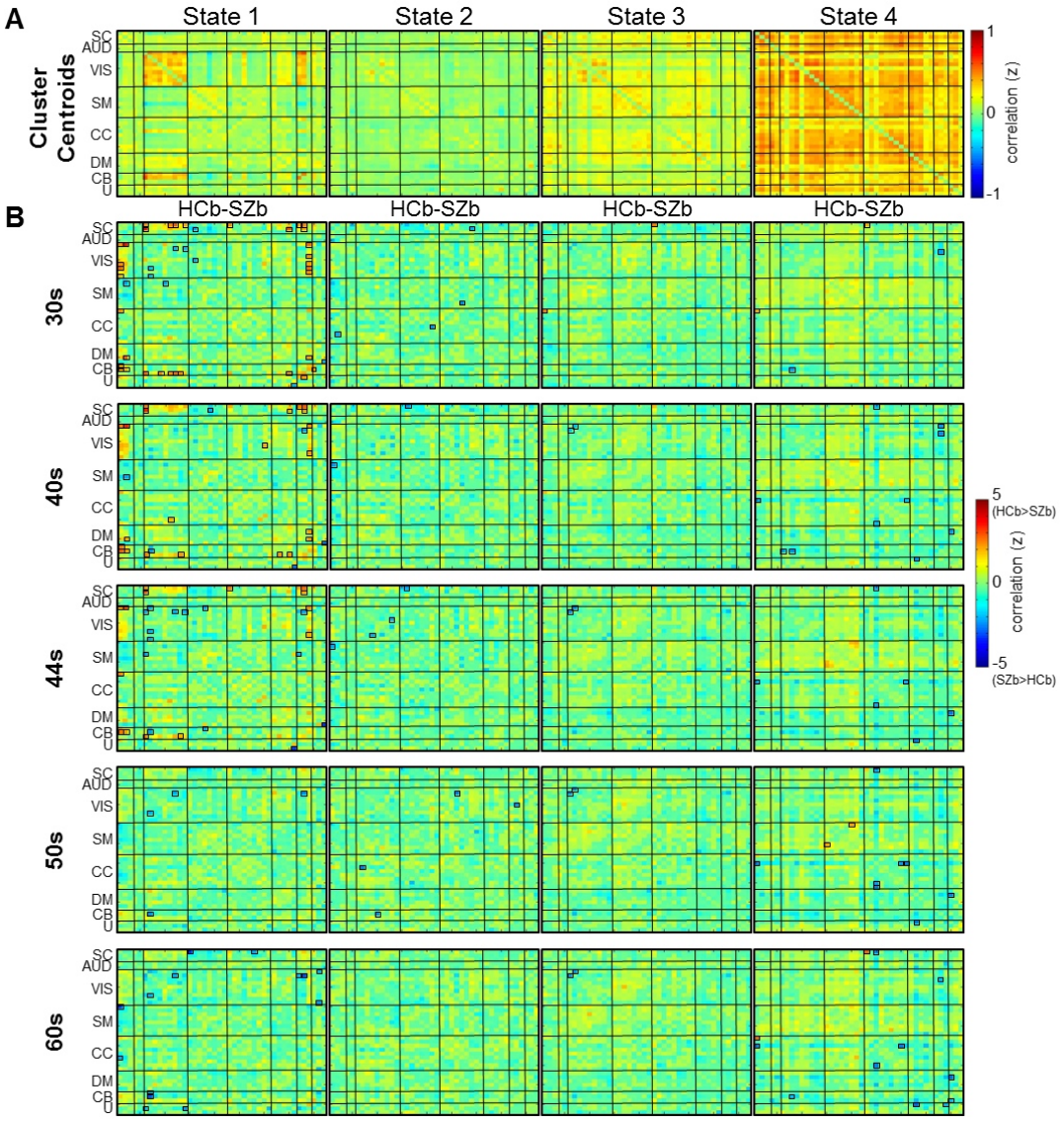

Figure 3: Dynamic functional network connectivity group differences between healthy controls and unmedicated patients. (A) Dynamic functional network connectivity cluster centroids from 30s window. See Figure S1 for cluster centroids for all window sizes. (B) Significant group differences [Healthy controls (HCb) - Unmedicated patients (SZb)] for each window size are outlined with a black box. Group differences (p<0.05) that occur in 95% of the 1000 bootstrap resamples are considered significant.

	State 1		State 2		State 3		State 4	
30s	5	17	2			1	1	1
40s	3	11	1		1		5	
44s	7	7	2		1		3	
50s	2		2		1		4	1
60s	7				1		5	1

Figure 4: Summary of group differences between healthy controls and unmedicated patients at all window sizes. Blue indicates increased connectivity in unmedicated patients compared to controls. Red indicates decreased connectivity in unmedicated patients compared to controls. Numbers indicate how many significant connections were found. Group differences ($p<0.05$) that occur in 95% of the 1000 bootstrap resamples are considered significant. Increasing intensity of color represents increasing number of significant connections.

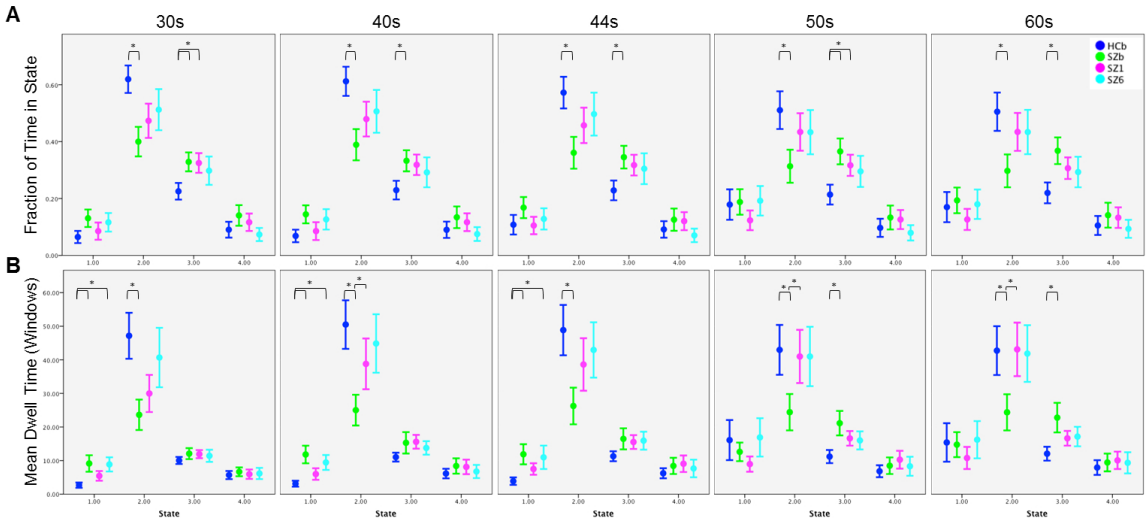

Figure 5: Connectivity state statistics. Exploratory post-hoc analysis of fraction of time (A) and mean dwell time (B) subjects spend in each state at each window size. Mean fraction of time groups spend in a state (A) and mean group dwell times (B) are depicted with error bars representing the standard error of the mean. Significant group differences (p<0.05) obtained via two-sample and paired t-tests are indicated with asterisks. HCb, healthy control; SZb, unmedicated patients; SZ1, week 1 medication treatment; SZ6, week 6 medication treatment.

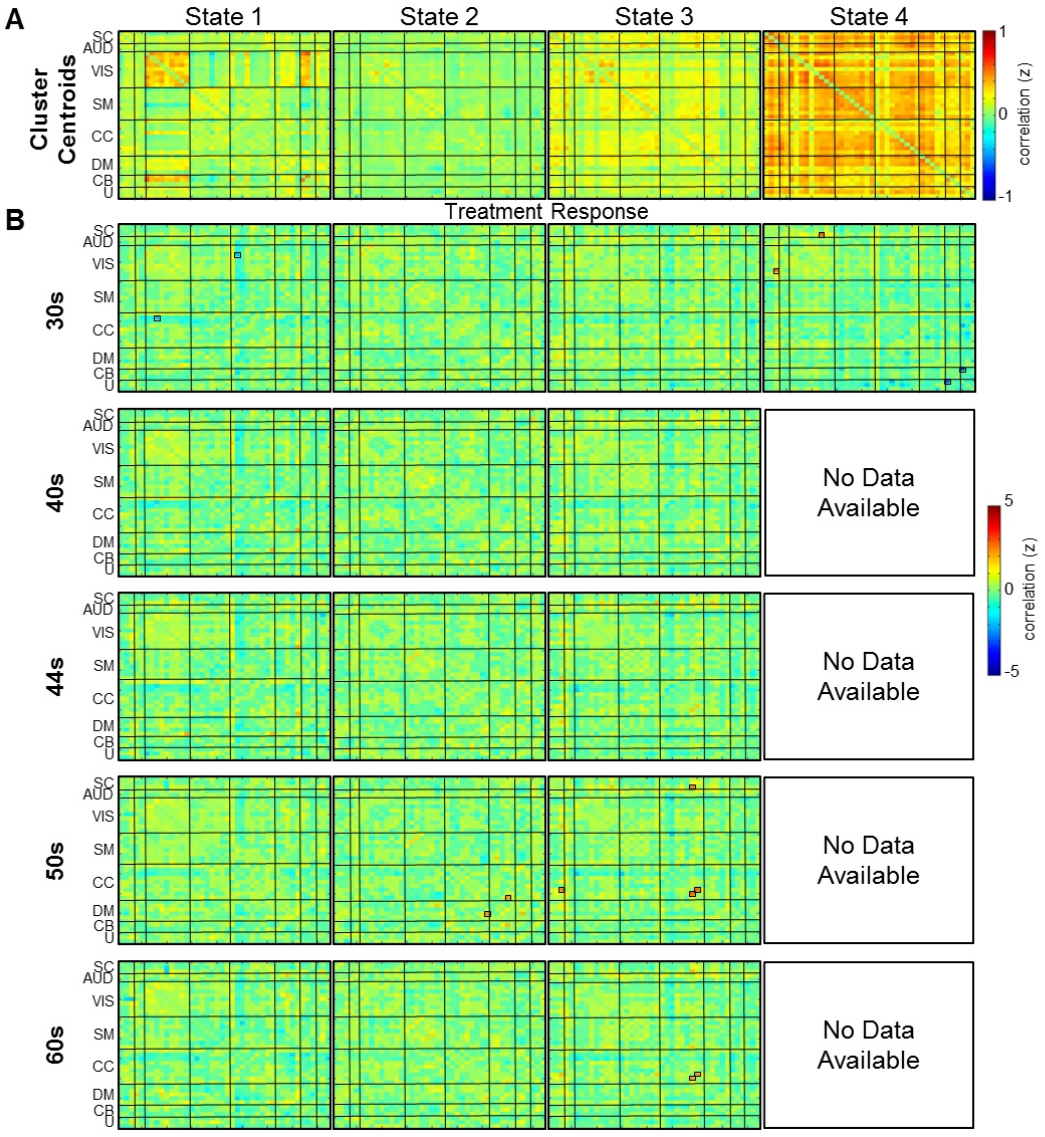

Figure 6: Relationship between treatment response and baseline dynamic functional connectivity. (A) dFNC cluster centroids from 30s window. See Figure S1 for cluster centroids for all window sizes. (B) Significant effects of treatment response on baseline dynamic connectivity. Group differences (p<0.05) that occur in 95% of the 10,000 bootstrap resamples are considered significant and outlined with a black box. Data was not available for state 4 at 40s, 44s, 50s, and 60s due to the small amount of subjects exhibiting state 4 and a minimum observation requirement of the regression algorithm.

Table S1: RSN Peak Activations

RSN regions	T_{max}	Peak Coordinates[a]		
		x	y	z
Subcortical networks				
IC 34 (0.977)[b]				
R putamen	21.85	18	13.5	-4.5
L putamen	20.32	-15	13.5	-3
IC 45 (0.973)				
Thalamus	20.18	13.5	-19.5	9
IC 50 (0.974)				
R putamen	21.91	25.5	4.5	3
L putamen	20.29	-25.5	6	1.5
Auditory networks				
IC 43 (0.975)				
R superior temporal gyrus	21.22	52.5	-28.5	12
L superior temporal gyrus	19.72	-51	-21	10.5
IC 86 (0.958)				
L middle temporal gyrus	22.39	-54	-40.5	6
Somatomotor networks				
IC 6 (0.983)				
R supplementary motor area	22.57	1.5	-22.5	60
IC 10 (0.983)				
R postcentral gyrus	24.87	55.5	-7.5	27
L postcentral gyrus	24.17	-52.5	-9	33
IC 31 (0.977)				
R postcentral gyrus	20.23	42	-27	46.5
IC 36 (0.975)				
L postcentral gyrus	21.28	-34.5	-22.5	51
R precentral gyrus	10.01	39	-16.5	49.5
IC 55 (0.971)				
R supplementary motor area	15.99	1.5	-1.5	49.5
IC 62 (0.971)				
R postcentral gyrus	14.95	24	-42	58.5
IC 75 (0.949)				
L inferior parietal lobule	18.17	-52.5	-27	37.5
R inferior parietal lobule	11.31	45	-39	51
IC 90 (0.914)				
L supplementary motor area	22.68	-3	10.5	52.5
Visual networks				
IC 8 (0.982)				
L middle occipital gyrus	19.49	-28.5	-88.5	4.5
IC 18 (0.979)				
Middle occipital gyrus	19.82	-31.5	-69	7.5
IC 25 (0.978)				
R calcarine gyrus	22.23	7.5	-78	3
IC 30 (0.978)				
L fusiform gyrus	19.88	-25.5	-61.5	-9
R fusiform gyrus	17.96	28.5	-60	-7.5
IC 32 (0.977)				
Middle occipital gyrus	17.99	33	-67.5	1.5
IC 33 (0.976)				
R cuneus	19.98	6	-79.5	21
IC 57 (0.969)				
R middle temporal gyrus	16.21	52.5	-58.5	6
L middle temporal gyrus	16.02	-48	-61.5	13.5
IC 58 (0.967)				

L calcarine gyrus	22.99	-12	-61.5	6
IC 79 (0.908)				
L cuneus	18.92	-16.5	-60	19.5
R fusiform gyrus	11.21	27	-39	-12
Cognitive control networks				
IC 15 (0.981)				
L superior frontal gyrus	15.47	-25.5	52.5	0
IC 42 (0.975)				
L angular gyrus	18.57	-45	-61.5	45
L inferior frontal gyrus	14.25	-42	46.5	1.5
L superior medial frontal gyrus	10.44	-3	34.5	36
IC 44 (0.976)				
R inferior parietal lobule	20.6	49.5	-54	42
R middle frontal gyrus	12.61	30	19.5	55.5
R middle cingulate cortex	11.11	6	-39	39
IC 46 (0.972)				
R angular gyrus	18.75	30	-61.5	42
L middle occipital gyrus	16.7	-22.5	-64.5	36
IC 48 (0.979)				
R middle frontal gyrus	16.71	31.5	54	16.5
L middle frontal gyrus	15.05	-28.5	49.5	10.5
IC 67 (0.960)				
R inferior frontal gyrus	20.03	49.5	15	24
L inferior frontal gyrus	14.17	-40.5	13.5	28.5
IC 70 (0.948)				
L inferior parietal lobule	15.77	-52.5	-48	37.5
R supramarginal gyrus	15.74	49.5	-45	24
IC 81 (0.943)				
R insula	17.95	39	19.5	-1.5
L insula	16.99	-37.5	13.5	-1.5
IC 94 (0.771)				
L hippocampus	17.91	-28.5	-24	-9
Superior temporal gyrus	11.48	48	3	-13.5
Default mode networks				
IC 24 (0.980)				
R precuneus	23.05	3	-58.5	48
IC 29 (0.976)				
L precuneus	25.45	-4.5	-69	33
IC 54 (0.969)				
L anterior cingulate cortex	21.49	1.5	37.5	13.5
IC 66 (0.960)				
R precuneus	26.48	1.5	-54	25.5
L angular gyrus	16.18	-49.5	-66	30
R angular gyrus	14.26	45	-60	28.5
IC 99 (0.581)				
L precuneus	20.32	-4.5	-46.5	9
Cerebellar networks				
IC 14 (0.979)				
L cerebellum	18.74	-4.5	-51	-45
IC 16 (0.983)				
R cerebellum crus1	18.29	37.5	-67.5	-27
IC 49 (0.979)				
L cerebellum crus1	14.61	-31.5	-66	-36
Unknown networks[c]				
IC 61 (0.968)				
R middle temporal gyrus	18.83	51	-37.5	3

IC 82 (0.931)				
L superior medial frontal gyrus	17.83	-1.5	42	48
IC 92 (0.913)				
Middle temporal gyrus	17.67	-43.5	-42	-3

Abbreviations: RSN, resting-state network; T_{max}, maximum cluster t-statistic; L, left; R, right.

[a]Coordinate (mm) of cluster peak activation in MNI space.

[b]Component number (Quality index - I_q) indicated

[c]A consensus on a network among the three reviewers could not be met with unknown network components. Input from additional neuroimagers necessary for a clear identification.

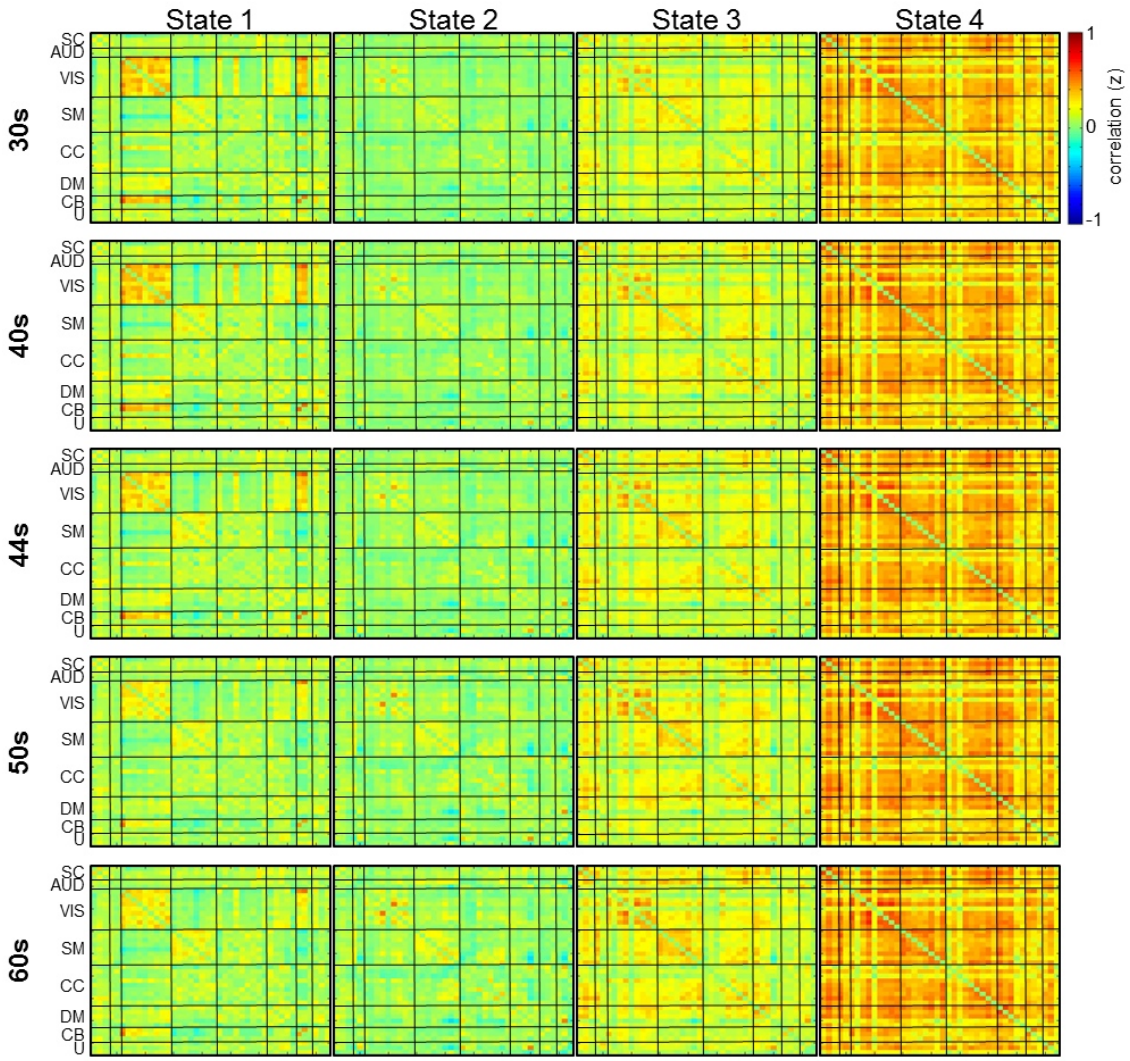

Figure S1: Cluster centroids for 30, 40, 44, 50 and 60s window sizes.

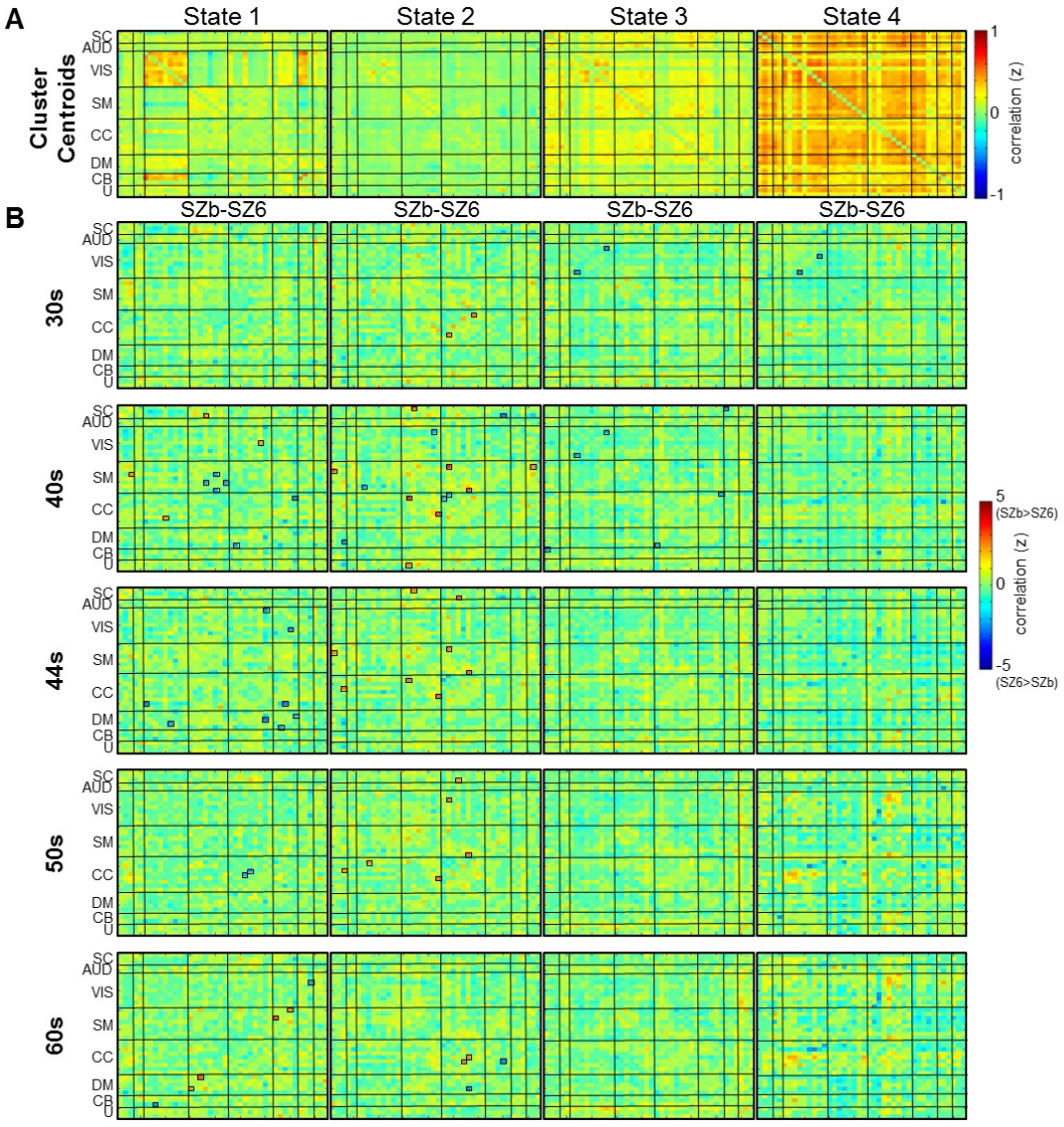

Figure S2: Dynamic functional network connectivity group differences between unmedicated and medicated patients. (A) Dynamic functional network connectivity cluster centroids from 30s window. See Figure S1 for cluster centroids for all window sizes. (B) Significant group differences [Unmedicated patients (SZb) – week 6 patients (SZ6)] for each window size are outlined with a black box. Group differences (p<0.05) that occur in 95% of the 1000 bootstrap resamples are considered significant.

CONCLUSIONS

The recent emergence of dynamic functional network connectivity has provided a new outlook for analyzing and interpreting network connectivity in patients with schizophrenia, as well as other mental disorders. The current literature has extensively evaluated network dysconnectivity via functional connectivity analyses in order to elucidate the pathology of the disorder. However, due to the inconsistencies in results from these static methods, clinical translation is deficient. In this work, we have extended the dysconnectivity concept of schizophrenia through demonstration of widespread state-dependent aberrant connectivity abnormalities in unmedicated patients. Unmedicated patients tended to spend a significantly shorter amount of time in a sparsely connected state than controls; however, risperidone treatment appears to reduce differences between controls and patients.

These results illustrate the importance of dynamically analyzing network connectivity, as static analyses blur the transient nature of network coherence and cannot provide critical information pertaining to state dwell times, transition probabilities, and state-dependent connectivity patterns. Ultimately, the utilization of dynamic functional network connectivity analyses provides not only greater insight into the role of network dysconnectivity in mental disorders such as schizophrenia, but also progress toward identification of imaging biomarkers characteristic of pathophysiological states.

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APPENDIX: INSTITUTIONAL REVIEW BOARD APPROVAL

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on November 24, 2003 and expires on October 26, 2010. The Assurance number is FWA00005960.

Principal Investigator:	LAHTI, ADRIENNE C.
Co-Investigator(s):	
Protocol Number:	**F080807011**
Protocol Title:	*Treatment Response in Schizophrenia: Bridging Imaging and Postmortem Studies*

The IRB reviewed and approved the above named project on 9/17/2008. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 9/17/2008

Date IRB Approval Issued: 10/09/08

Identification Number: IRB00000726

Ferdinand Urthaler, MD

Ferdinand Urthaler, M.D.
Chairman of the Institutional Review
Board for Human Use (IRB)

Partial HIPAA Waiver Approved?: Yes

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

470 Administration Building
701 20th Street South
205.934.3789
Fax 205.934.1301
irb@uab.edu

The University of
Alabama at Birmingham
Mailing Address:
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1530 3RD AVE S
BIRMINGHAM AL 35294-0104

OMB No. 0990-0263
Approved for use through 3/31/2015

Protection of Human Subjects
Assurance Identification/IRB Certification/Declaration of Exemption
(Common Rule)

Policy: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the Common Rule. See section 101(b) of the Common Rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the Common Rule. Institutions must have an assurance of compliance that applies to the research to be conducted and should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency.

1. Request Type	2. Type of Mechanism	3. Name of Federal Department or Agency and, if known, Application or Proposal Identification No.
[ ] ORIGINAL [X] CONTINUATION [ ] EXEMPTION	[X] GRANT [ ] CONTRACT [ ] FELLOWSHIP [ ] COOPERATIVE AGREEMENT [ ] OTHER:_____	
4. Title of Application or Activity Treatment Response in Schizophrenia: Bridging Imaging and Postmortem Studies		5. Name of Principal Investigator, Program Director, Fellow, or Other LAHTI, ADRIENNE C.

6. Assurance Status of this Project *(Respond to one of the following)*

[X] This Assurance, on file with Department of Health and Human Services, covers this activity:
Assurance Identification No. FWA00005960 , the expiration date 01/24/2017 IRB Registration No. IRB00000196

[ ] This Assurance, on file with *(agency/dept)*_____, covers this activity.
Assurance No._____, the expiration date_____ IRB Registration/Identification No._____*(if applicable)*

[ ] No assurance has been filed for this institution. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

[ ] Exemption Status: Human subjects are involved, but this activity qualifies for exemption under Section 101(b), paragraph_____.

7. Certification of IRB Review (Respond to one of the following IF you have an Assurance on file)

[X] This activity has been reviewed and approved by the IRB in accordance with the Common Rule and any other governing regulations.
by: [X] Full IRB Review on (date of IRB meeting) 4/29/2015 or [ ] Expedited Review on (date) _____
[ ] If less than one year approval, provide expiration date _____

[ ] This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the Common Rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments	Title F080807011
Protocol subject to Annual continuing review. Partial HIPAA Waiver Approved?: Yes	Treatment Response in Schizophrenia: Bridging Imaging and Postmortem Studies
IRB Approval Issued: 5/6/15	IRB Approval No Longer Valid On: 4/29/16

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed until study closure and certification will be provided.	10. Name and Address of Institution University of Alabama at Birmingham 701 20th Street South Birmingham, AL 35294
11. Phone No. *(with area code)* (205) 934-3789 12. Fax No. *(with area code)* (205) 934-1301 13. Email: irb@uab.edu	
14. Name of Official Ferdinand Urthaler, M.D.	15. Title Chairman, IRB
16. Signature Ferdinand Urthaler MD/cw	17. Date 5/6/15

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

PI: LAHTI, ADRIENNE C.
Protocol # F080807011

UAB IRB Approval of Partial Waiver of HIPAA Authorization to Use PHI in Screening for Research

☒ **Patient Authorization: Approval of Partial HIPAA Waiver to Use PHI in Screening for Research.** The IRB reviewed the proposed research and granted the request for a "partial HIPAA waiver," to allow the proposed use of protected health information (PHI) in screening for research, based on the following findings:

1. The use/disclosure of PHI to screen candidates for research involves no more than minimal risk to the privacy of individuals
   a. There is an adequate plan to protect the identifiers from improper use and disclosure.
   b. There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
   c. The PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.
2. The screening cannot practicably be conducted without the waiver or alteration.
3. The screening cannot practicably be conducted without access to and use of the PHI.

—OR—

☒ **Full Review**

The IRB reviewed the proposed research at a **convened meeting** at which a majority of the IRB was present, including one member who is not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities. The partial waiver of authorization for screening was approved by the majority of the IRB members present at the meeting.

4/29/15
Date of Meeting

Ferdinand Urbahn MD/as
Signature of Chair, Vice-Chair or Designee

5/6/15
Date

☐ **Expedited Review**

The IRB used an **expedited review procedure** because the research involves no more than minimal risk to the privacy of the individuals who are the subject of the PHI for which use or disclosure is being sought. The review and approval of the partial waiver of authorization for screening was carried out by the Chair of the IRB, or by one of the Vice-Chairs of the IRB as designated by the Chair of the IRB.

_____
Date of Expedited Review

_____
Signature of Chair, Vice-Chair or Designee

_____
Date

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UAB Project Revision/Amendment Form

irb

Form version: June 26, 2012

In MS Word, click in the white boxes and type your text; double-click checkboxes to check/uncheck.

- **Federal regulations require IRB approval before implementing proposed changes. See Section 14 of the IRB Guidebook for Investigators for additional information.**
- **Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the investigator's Brochure, questionnaires, surveys, advertisements, etc.). See Item 4 for more examples.**

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OCT 21 2014
OFFICE OF INSTITUTIONAL REVIEW BOARD

7630

1. Today's Date	10/21/14

2. Principal Investigator (PI)

Name (with degree)	Adrienne C. Lahti, M.D.	Blazer ID	alahti
Department	Psychiatry & Behavioral Neurobiology	Division (if applicable)	
Office Address	SC 501	Office Phone	6-6776
E-mail	alahti@uab.edu	Fax Number	

Contact person who should receive copies of IRB correspondence (Optional)

Name	David M. White MPH MPA	E-Mail	dw2777@uab.edu
Phone	69813	Fax Number	
Office Address (if different from PI)			

3. UAB IRB Protocol Identification

3.a. Protocol Number	F080807011
3.b. Protocol Title	Treatment response in schizophrenia: bridging imaging and postmortem studies

3.c. Current Status of Protocol—Check ONE box at left; provide numbers and dates where applicable

- ☐ Study has not yet begun — No participants, data, or specimens have been entered.
- ☒ In progress, open to accrual — Number of participants, data, or specimens entered: 90
- ☐ Enrollment temporarily suspended by sponsor
- ☐ Closed to accrual, but procedures continue as defined in the protocol (therapy, intervention, follow-up visits, etc.)
  - Date closed:
  - Number of participants receiving interventions:
  - Number of participants in long-term follow-up only:
- ☐ Closed to accrual, and only data analysis continues
  - Date closed:
  - Total number of participants entered:

4. Types of Change

Check all types of change that apply, and describe the changes in Item 5.c. or 5.d. as applicable. To help avoid delay in IRB review, please ensure that you provide the required materials and/or information for each type of change checked.

- ☐ **Protocol revision (change in the IRB-approved protocol)**
  In Item 5.c., if applicable, provide sponsor's protocol version number, amendment number, update number, etc.
- ☐ **Protocol amendment (addition to the IRB-approved protocol)**
  In Item 5.c., if applicable, provide funding application document from sponsor, as well as sponsor's protocol version number, amendment number, update number, etc.
- ☒ **Add or remove personnel**
  In Item 5.c., include name, title/degree, department/division, institutional affiliation, and role(s) in research, and address whether new personnel have any conflict of interest. See "Change in Principal Investigator" in the IRB Guidebook if the principal investigator is being changed.
  - ☐ **Add graduate student(s) or postdoctoral fellow(s) working toward thesis, dissertation, or publication**
    In Item 5.c., (a) identify these individuals by name; (b) provide the working title of the thesis, dissertation, or publication; and (c) indicate whether or not the student's analysis differs in any way from the purpose of the research described in the IRB-approved HSP (e.g., a secondary analysis of data obtained under this HSP).
- ☐ **Change in source of funding; change or add funding**
  In Item 5.c., describe the change or addition in detail, include the applicable OSP proposal number(s), and provide a copy of the application as funded (or as submitted to the sponsor if pending). Note that some changes in funding may require a new IRB application.

☐	**Add or remove performance sites** In Item 5.c., identify the site and location, and describe the research-related procedures performed there. If adding site(s), attach notification of permission or IRB approval to perform research there. Also include copy of subcontract, if applicable. If this protocol includes acting as the Coordinating Center for a study, attach IRB approval from any non-UAB site added.
☐	**Add or change a genetic component or storage of samples and/or data component—this could include data submissions for Genome-Wide Association Studies (GWAS)** To assist you in revising or preparing your submission, please see the IRB Guidebook for Investigators or call the IRB office at 934-3789.
☐	**Suspend, re-open, or permanently close protocol to accrual of individuals, data, or samples (IRB approval to remain active)** In Item 5.c., indicate the action, provide applicable dates and reasons for action; attach supporting documentation.
☐	**Report being forwarded to IRB (e.g., DSMB, sponsor or other monitor)** In Item 5.c., include date and source of report, summarize findings, and indicate any recommendations.
☐	**Revise or amend consent, assent form(s)** Complete Item 5.d.
☐	**Addendum (new) consent form** Complete Item 5.d.
☐	**Add or revise recruitment materials** Complete Item 5.d.
☐	**Other (e.g., investigator brochure)** Indicate the type of change in the space below, and provide details in Item 5.c. or 5.d. as applicable. Include a copy of all affected documents, with revisions highlighted as applicable.

▶

5. Description and Rationale

In Item 5.a. and 5.b, check Yes **or** No **and see instructions for** Yes **responses.**
In Item 5.c. and 5.d, describe—and explain the reason for—the change(s) noted in Item 4.

☒Yes ☐No	**5.a. Are any of the participants enrolled as normal, healthy controls?** If yes, describe in detail in Item 5.c. how this change will affect those participants.
☐Yes ☒No	**5.b. Does the change affect subject participation, such as procedures, risks, costs, location of services, etc.?** If yes, FAP-designated units complete a FAP submission and send to fap@uab.edu. Identify the FAP-designated unit in Item 5.c. For more details on the UAB FAP, see www.uab.edu/cto.

5.c. Protocol Changes: In the space below, briefly describe—and explain the reason for—all change(s) to the protocol.

▶ We would like to add Graduate Student Trainee Kirsten Schoonover, Graduate Research Assistants Elyse Cadena and Kristin Lottman, and Office Associate Racheal McKinney to the protocol.

5.d. Consent and Recruitment Changes: In the space below,
(a) describe all changes to IRB-approved forms or recruitment materials and the reasons for them;
(b) describe the reasons for the addition of any materials (e.g., addendum consent, recruitment); and
(c) indicate either how and when you will reconsent enrolled participants or why reconsenting is not necessary (not applicable for recruitment materials).

Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:
- **a copy of the currently approved document (showing the IRB approval stamp, if applicable)**
- **a revised copy highlighting all proposed changes with "tracked" changes**
- **a revised copy for the IRB approval stamp.**

▶

Signature of Principal Investigator [signature] Date 10/21/14

FOR IRB USE ONLY

☐ Received & Noted ☑ Approved Expedited* ☐ To Convened IRB

Sally Blake Headley, CIP — 11/11/14

Signature (Chair, Vice-Chair, Designee) Date

DOLA 5-7-14

Change to Expedited Category Y / N / NA

*No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 56.111