**TITLE:** Functional Connectivity as a Means to Delineate Differences between Treatment Resistant and Treatment Responsive Schizophrenia

**AUTHOR AND AFFILIATION:** Sara Paul¹ and Nathan Sharfman¹

¹Tulane University, Neuroscience Program

**CORRESPONDING AUTHOR INFORMATION:**

Nathan Sharfman

nsharfma@tulane.edu

6823 St. Charles Avenue, New Orleans, LA 70118

901-239-5688
Abstract:

It has been estimated that a third of schizophrenia patients are treatment resistant (TRS). Recent studies show that functional connectivity (FC) can be used for measuring connections between brain regions in diseased states. White and colleagues used FC to identify differences between schizophrenia patients responding to antipsychotic treatment and TRS patients. Their results support the idea that the groups differ not only in treatment response but also neurophysiologically through differences in FC.

Schizophrenia encompasses a wide range of symptoms and can be divided into three categories: positive, negative, and cognitive. (Fornito et al., 2013; Kapur, 2003; van den Heuvel & Fornito, 2014). Positive symptoms are auditory and visual hallucinations, perceptions, delusions, and atypical beliefs (van den Heuvel & Fornito, 2014), whereas negative symptoms involve social withdrawal, neglect, and loss of motivation (Kapur, 2003). Current treatments involve a variety of anti-psychotic medications that primarily function as dopamine antagonists, but also possess additional antagonist properties against the cholinergic, serotonergic and adrenergic systems (Heinz & Schlagenhauf, 2010). Currently, the main drug to treat these patients is Clozapine, a second-generation atypical antipsychotic medication that is a broad-acting antagonist targeting NMDA receptors, serotonergic receptors, α-adrenergic receptors and acetylcholine receptors (Elkis 2007). However, approximately 20-30% of patients are unresponsive to these drugs and considered to have treatment resistant schizophrenia (TRS). TRS patients experience auditory and visual hallucinations uncontrolled by pharmacological treatments (Nakajima et al., 2015). Attempts have been made to characterize the underlying neurophysiology of schizophrenia to better understand this illness and possibly find a biomarker associated with TRS. In the discussed paper, White and colleagues use functional imaging to identify functional connectivity (FC) differences within the striatal pathway and reveal different neurophysiology between the treatment-responsive and resistant groups.

Many techniques have been used to probe and identify morphology, connectivity, and broad global communication in schizophrenia, including diffuse weighted imaging, graph theory, and FC (van den Heuvel & Fornito, 2014). Recently, efforts have been aimed specifically at characterizing differences in neurophysiological pathways between individuals who respond to treatment and TRS patients. Such efforts may reveal differentially affected neural substrates between treatment responsive schizophrenia and TRS. Results of these studies may explain why current treatments are inefficacious in this subset of patients (Sarpal, Argyelan, et al., 2015). Through FC analysis, it may become apparent that TRS patients possess differentially affected neurophysiology revealing novel targets and providing further insight into TRS.

The symptoms of schizophrenia, particularly the positive symptoms, may be related to aberrant activity in striatum, and striatal dopamine levels have been shown to be elevated in schizophrenia (Fornito et al., 2013). In striatal system, dopamine controls reward, goal mediated behavior, anticipation of reward, and possibly salience acquisition (Haber &
Knutson, 2010; Kapur, 2003). In addition, dopamine is implicated in the default mode network (DMN), which is essentially the restful state of the brain (Garrity et al., 2007). Disruption of the DMN and dopaminergic pathways that include the mesolimbic and corticostriatal systems, are believed to lead to delusions and hallucinations (Garrity et al., 2007). Increased dopamine levels and oscillatory activity in regions of the DMN such as the hippocampus, parahippocampus, and cingulate gyrus (Garrity et al., 2007) may cause saliency attachment to inappropriate stimuli leading to psychotic symptoms (Kapur, 2003). Dysfunction within the DMN in schizophrenia is supported through MRI and FC studies, where there is decreased anatomical connectivity between the parietal regions and the prefrontal cortex (PFC) and increased connectivity between the ventral caudate and insular regions (Fornito et al., 2013; Skudlarski et al., 2010). The dorsal caudate modulates activity of the ventral caudate (Fornito et al., 2013), controlling signaling preferentially through GABAergic neurons (Haber & Knutson, 2010). A recent study demonstrated decreased connectivity between the dorsal caudate and PFC and increased connectivity between the ventral caudate and PFC (Fornito et al., 2013). Decreased connectivity of the dorsal corticostriatal pathway may alter modulation of the ventral corticostriatal pathway and lead to greater striatal dopamine, which has been observed in patients (Fornito et al., 2013). As previously mentioned, the increase in dopamine is related to psychosis and thus makes a preferable target for treatment.

Using FC, data analysis can be used to identify disease specific changes (Fornito et al., 2013), measure of treatment outcome (Sarpal, Argyelan, et al., 2015), and may be combined with anatomical data to yield more useful information about changes to brain areas in schizophrenia (Skudlarski et al., 2010). Importantly, similar patterns of connectivity are seen in first relatives of individuals with schizophrenia, implying a genetic aspect to schizophrenia that is associated with altered brain states. Furthermore, using FC analysis Fornito and colleges detected disease-specific differences between relatives and individuals, specifically in schizophrenia patients there was increased FC between the ventral caudate and the dorsolateral PFC (Fornito et al., 2013). In addition, FC may reflect changes in disease state in response to treatment, whereby increases between regions that were hypoconnected and decreases between regions that were hyperconnected in patients with a first episode of schizophrenia showed concomitant improvement with treatment (Sarpal, Robinson, et al., 2015). Taken together, FC analysis can be used to identify disease specific differences between patients with schizophrenia and patients without schizophrenia, reveal genetic components of schizophrenia using related family members, and may be used to identify efficacy of treatment as well.

Unfortunately, little research has been done looking differences between treatment responsive patients and TRS patients using FC (Nakajima et al., 2015). Auditory verbal hallucinations (AVH) are persistent hallucinations and up to a quarter of those with AVH may have TRS (Alonso-Solis et al., 2015). One study utilized patients with AVH and examined FC differences in the DMN between TRS and treatment responsive patients (Alonso-Solis et al., 2015). Their results revealed that the DMN was more active in patients with AVH. Indeed, increased activity in the DMN is associated with greater
psychosis (Alonso-Solis et al., 2015). Of importance, patients with AVH had increased
disruption between the two subsets of schizophrenia patients using FC analysis. The
efforts put forth by White and colleagues were threefold: First, they investigated the
differences in corticostriatal FC between treatment responsive and TRS patients. They
targeted the corticostriatal pathway as the striatum is involved in various processes,
including learning and has densely innervated dopaminergic pathways (Haber &
Knutson, 2010). Secondly, they compared differences in connectivity between treatment
responsive and TRS patients to controls to investigate differences in fronto-spatial
disruption in Schizophrenia. There have been multitudes of imaging studies
comparing schizophrenia patients to controls (for review see Nakajima et al., 2015), yet
White and colleagues compared the groups against controls to further identify differences
between treatment responsive and TRS patients. Finally, they investigated the
relationship between positive symptoms and connectivity between groups to see if
positive symptoms predicted FC differences.

White and colleagues found that the TRS patients exhibited increased connectivity in the
dorsal caudate with the medial and superior PFC. In addition, White and colleagues
observed decreased connectivity between the ventral striatum and substantia nigra, and
between the dorsal caudate and the pulvinar of the thalamus in TRS patients compared to
treatment responsive patients (Fig. 1). Increased positive symptoms were associated with
decreased connectivity between the ventral striatum and both the precuneus and
cingulate. In addition, greater positive symptom severity was associated with increased
connectivity between the dorsal striatum and precuneus, posterior cingulate and medial
PFC. Finally, anti-psychotic dose was found to inversely predict FC, mainly within the
ventral stratum, however direct comparisons between groups were not performed due to
methodological limitations.

In light of these findings, White and colleagues conclude that the ventral striatum and
substantia nigra hypoconnectivity may contribute to a potential mechanism for TRS. The
ventral striatum is a key region that projects both the substantia nigra compacta and the
reticulata (Haber & Knutson, 2010). The ventral striatum forms a loop by projecting to
the substantia nigra compacta and reticulata, which in turn projects back to the dorsal
striatum (Haber & Knutson, 2010). This essentially forms feedback loops starting with
the ventral striatum, progressing to the dorsal striatum that are organized topographically
across the substantia nigra forming striato-nigro-striatal connections. Given the wide
range of projections of the ventral striatum and dorsal striatum, their role in learning, and
the implications in saliency (Haber & Knutson, 2010), any decoupling between these
regions is likely to have larger implications on global functioning. Furthermore, White
and colleagues reported hyperconnectivity between the dorsal striatum, precuneus, and inferior parietal lobe, associated with increased positive symptom severity. This is consistent with previous research that showed decoupling of this network is associated with increased positive symptoms (Alonso-Solis et al., 2015; Fornito et al., 2013; Garrity et al., 2007). Taken together, the findings from White and colleagues indicate that there are differences in connectivity that distinguish between TRS and treatment responsive patients, and that decoupling of connectivity within the DMN is associated with increased positive symptoms that may be related to TRS.

Despite the characterization of TRS, to date no longitudinal studies have investigated changes in TRS using FC. To understand this disorder in full, understanding changes that occur over time are critical, as biomarkers may be discovered that allow for preferential treatment to TRS (Fornito et al., 2013; Sarpal, Robinson, et al., 2015). Additionally, some studies have investigated anti-psychotic treatment and changes to FC with treatment responsive schizophrenia patients (Sarpal et al., 2015), however this has yet to be done with TRS, limiting the potential power of FC as an investigational tool. Also, FC offers limited insight into the underlying mechanisms of differences in connectivity. Therefore, using anatomical methods such as DTI and FC in treatment responsive and TRS patients (Skudlarski et al., 2010) may offer increased resolution of affected pathways. Admittedly, it should be noted that neuroimaging studies have limitations, which may explain some discrepant findings. For instance, corticostriatal connectivity between the ventral striatum and the dorsomedial PFC (dmPFC) has been reported to be both increased (Fornito et al., 2013) and decreased (White et al., 2015). White and colleagues offer insight into nigrostriatal decoupling between TRS and treatment responsive schizophrenia, and their findings may be beneficial as biomarkers for predicting individuals who are more unlikely to respond to medication. Clearly, there are differences in nigrostriatal and corticostriatal systems between treatment responsive and TRS patients, and future studies are needed to find other regions that may be affected in TRS and determine the reasons for the connectivity dysregulation.

One potential future brain area that may offer insight into TRS is the insula. The insula is a critical structure coupled with the cingulate cortex that modulates both bottom-up and top-down processing of stimuli, playing a key role in attributing saliency to appropriate stimuli (Menon & Uddin, 2010). Specifically, the anterior insula and the anterior cingulate cortex (ACC) compose the saliency network (SN). The SN integrates bottom up sensory processes, controls top down output, and more importantly as shown by Granger causality analysis, controls the switch from a restful state, or DMN, to attentive state, or the central executive network (CEN) (Menon & Uddin, 2010; Sridharan, Levitin, & Menon, 2008). Dysfunction of the saliency network may underlie psychosis and has been found in studies of schizophrenia. For example, ACC connectivity is affected in schizophrenia (Garrity et al., 2007; Sarpal, Robinson, et al., 2015; Skudlarski et al., 2010), implicating dysfunction of the SN. Furthermore, regions of the SN are associated with TRS markers including AVH (Alonso-Solis et al., 2015) and positive symptoms (White et al., 2015). In patients with AVH, there is increased FC with the insular cortex and dmPFC, a critical region of the CEN (Alonso-Solis et al., 2015; Menon & Uddin,
2010) suggesting changes in these regions may partially underlie the etiology of TRS. Taken together, the evidence presented here indicates differentially affected neurophysiology between TRS and treatment responsive patients, and that future studies are needed to characterize other potential regions and systems in TRS, such as the insula cortex and the saliency network.

References:

286
287
Figure 1: Regional Functional Connectivity Differences of Treatment Resistant Schizophrenics Compared to Treatment Responsive Schizophrenics