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Neurological Discrepancies between Bipolar Disorder, Schizophrenia and Schizoaffective Disorder

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TRINITY COLLEGE

NEUROLOGICAL DISCREPANCIES BETWEEN BIPOLAR DISORDER,
SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

BY
Nat Bush

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Neurological Discrepancies between Bipolar Disorder,
Schizophrenia and Schizoaffective Disorder

BY
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Neurological Discrepancies between Bipolar Disorder, Schizophrenia and Schizoaffective Disorder

Introduction

As neurological research advances, so does the understanding of how disorders and diseases develop and how they can be treated. The debate of how mental disorders develop has been ongoing and complicated, as there is still no clear understanding of whether disorders are caused by genetic or neurological predispositions, familial upbringing, or whether they arise as one matures and a life occurrence triggers the onset. Understanding the cause of a disorder is crucial to determining how to treat it. For example, for a long time psychologists tried to convince society that suicidal depression is solely caused by a deficiency in serotonin, but plenty of research has provided counterarguments that there is a complex distinction in brain activity in people with depression as opposed to healthy individuals (Lacasse & Leo, 2005). As a result of this research, the way in which depression is treated has improved, as there is a more obvious importance of combining medication and psychotherapy in various intensities based on the individual's needs. Other disorders have been identified as needing more nuanced treatment plans, and some of these disorders have been identified as somewhat similar in their characteristics and forms of treatment. Three disorders in particular have been highlighted for sharing brain functioning patterns and symptoms: bipolar disorder (BPD), schizophrenia (SZP), and schizoaffective disorder (SAD).

The research conducted in this thesis is part of an ongoing study at the Olin Neuropsychiatric Research Institute (ONRC) at the Institute of Living in Hartford, CT called the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Researchers across the

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United States are included in the B-SNIP study to determine the biological explanation for the development of BPD, SZP, and SAD (Tamminga et al., 2013).

Psychological Symptoms of BPD, SZP, and SAD

BPD is characterized by fluctuations between depression and mania, with transitions ranging from days to months. In depressive states, the individual may have little interest in regular daily activities and they may become more reclusive. In manic states, an individual may become more creative and impulsive; they may be more inclined to participate in reckless activities such as gambling and drugs or use creative outlets such as painting or playing music.

SZP is a disorder that still has no known cure. It is characterized by the addition of symptoms atypical of normal behavior (positive symptoms) and removal of typical symptoms (negative symptoms). Positive symptoms include delusions, hallucinations, and thought disorder, whereas negative symptoms include a lack of affect, social isolation, and memory loss. Finally, SAD is characterized by fluctuations between severe and more subdued symptoms, including hallucinations, delusions, low interest in daily activities, impulsivity, and reduced emotions. It is typically diagnosed if the individual exhibits both SZP symptoms and symptoms of a mood disorder such as depression.

As one can see, these disorders share many symptoms. BPD and SAD both have swings between high and low mood and motivation. SZP and SAD both have delusions and hallucinations. Arguably, one can say that BPD and SZP are also very similar in that they both display low moods and social isolation at times, which are indicators of depression. With these similar symptoms, one can predict that there is similar brain activity between these disorders, and

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the difference in brain activity when compared to control groups is likely similar. SAD has been theorized to be either a variant of the other two disorders or to be a part of a spectrum of psychotic mood disorders (Mancuso et al., 2015). Over the past couple decades, many studies, some of which will be introduced later, have been conducted to attempt to come to a concise agreement on the distinction between these disorders, or lack thereof. Though the results of these studies generally found clear differences reinforcing the distinctions between these disorders, the explanations for their cause is still unclear.

Treatment of BPD, SZP, and SAD

Since the cause of these disorders is still not confirmed, the best method of treatment is also not yet known. This is the main concern regarding research on the neurological cause of BPD, SZP, and SAD. These disorders individually affect 0.5% to 1% of the United States population. Though some patients do receive successful treatment, there are still individuals who may be misdiagnosed, and thus treated improperly. For example, in a study conducted by Cascade et al. (2009), they found that 22% of individuals with SAD only receive antipsychotics, 20% receive both antipsychotics and mood medication, and 18% receive antipsychotic, mood, and antidepressant medication. Other individuals receive even more medications to account for anxiety or other problems. Since it is still unclear whether SAD should even be considered an entirely distinct disorder in the DSM, it is also unclear whether the best form of treatment is related to that of SZP or BPD, and therefore individuals with SAD can receive a range from one to even five medications for the one disorder. It is not sustainable for an individual to be so heavily dependent on multiple medications in order to lead a normal life.

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The symptoms and neurological functioning of BPD is better understood, but the range of treatments still varies greatly as well. A study conducted by Jann (2014) found that over 75% of individuals with BPD take their medication less than 75% of the time. Although mood stabilizers, such as lithium, tend to be the main form of treatment for the disorder, atypical antipsychotics are also occasionally used. This range of treatments is generally caused by the range in manic and depressive symptoms that each individual experiences.

Finally, individuals with SZP are generally recommended to follow a well-regulated pathway of treatment. According to Patel et al. (2014), drug treatment and therapy should start as soon as possible after the first psychotic episode occurs. Second-generation atypical antipsychotics are typical for the first medication. Starting a combination of medications is only recommended in the later stages of the disorder development. However, 10-30% of individuals with SZP appear to be resistant to the effects of antipsychotic medication, and thus Clozapine is recommended, though individuals who take this medication have to be carefully monitored for the risk of developing hypotension.

The form of treatment for each disorder depends on the symptoms and individuality of each patient, but this also means that the pathway to becoming healthy is different for every individual. Some people cannot be treated easily, which is unfair to them. Just because an individual's neurological and psychological functioning are impaired, it does not mean that they are individuals incapable of participating as active citizens of their communities. The goal of research such as that which is conducted in this thesis is to further assist in allowing individuals with these disorders to live healthy lives. Since the pattern of neurological functioning of each disorder is still unclear, psychiatrists cannot yet provide individuals with a

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clear form of treatment to target those neurological impairments and allow them to be healthy again.

Previous findings of neurological differences

The cause and method of treatment is still a mystery for SZP. There does appear to be significant disruption in functional connectivity in the prefrontal and medial temporal lobes, which are involved in working memory and declarative memory, but this could be caused by any combination of genetic and environmental factors (Karlsgodt et al., 2010). Another study found strong evidence for abnormalities in the hippocampus and ventricles and for deficiencies in the prefrontal cortex, but the risk factors for these problems also ranges from genetics to stressful life encounters (Lawrie et al., 2008). No single conclusive results have been found yet to explain what is specifically neurologically different for individuals with SZP as opposed to individuals who are neurologically healthy or who have a different disorder.

BPD is a bit easier to treat due to a generally effective method of treatment and clear characteristics of symptoms, though the neurological predisposition for the disorder is not yet clear either. Some previous studies have found possible abnormalities in the prefrontal cortex, striatum, and amygdala, and abnormalities in the cerebellar vermis and lateral ventricles can develop later in life. The most substantial regions, however, to be functioning improperly is the amygdala and other portions of the limbic network (Strakowski et al., 2005). It makes sense that the brain regions involved in mood regulation are impacted in individuals with BPD, though not all individuals with the disorder exhibit these neurological distinctions.

SAD is particularly difficult to understand as there are not yet many studies that have found any conclusive evidence on what makes the disorder neurologically distinct from BPD and

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SZP. Articles on SAD generally redirect to those that only pertain to SZP, or they can include both SAD and SZP in the article title but only discuss SZP in the majority of the results, such as one article by Hoptman et al. (2005).

For the purpose of this thesis, it is necessary to analyze any type of overlap or differences in neurological functioning between the disorders. Some previous studies have indeed found some neurological similarities. One study compared the neurological differences between SZP and BPD in a meta-analysis. They found 17 resultant ALE clusters, and both disorders exhibited lower gray matter in the bilateral frontal gyrus, thalamus, left middle temporal gyrus, cingulate gyrus, and caudate. Only SZP displayed reduced gray matter volume in the left amygdala and insula, which led to the conclusion that both disorders have reduced gray matter volume in regions throughout the brain, but SZP has additional reduced gray matter in the left hemisphere (Yu et al., 2010). These reductions in volume may explain the negative impact on mood regulation present in both disorders, particularly in SZP. Another study compared the biological distinctions between BPD and SZP – the researchers found a lot of similarities in the risk loci, but the copy number variation is less obvious in BPD (Harrison et al., 2018). These results indicate that at the chromosomal level, the disorders exhibit similar differences in the gene variation when compared to control groups, so it is possible that the biological reason for both disorders is the same.

Since the analyses conducted in this thesis involve the functional connectivity of the disorders, it is also necessary to see what previous researchers have found on the brain connectivity of these disorders. Argyelan et al. (2014) studied resting-state fMRI images of BPD and SZP. They found that individuals with SZP exhibit significantly lower overall connectivity

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between brain regions when compared to the control group, and BPD subjects had some connectivity reduction, but this was more subdued from that of SZP subjects.

Finally, another group of researchers attempted to determine similarities in SAD and the other two disorders. SAD was introduced as a distinct disorder 80 years ago, but the symptoms and characteristics of the disorder are so similar to those of the other two so there is still debate on whether it should be its own disorder, something between the two other disorders, or not an official disorder at all. A paper written by Ellison-Wright and Bullmore (2010) analyzed 42 studies of subjects with SZP and BPD. They found gray matter volume reduction in SZP in the frontal, temporal, cingulate, and insular cortices and the thalamus, and increased gray matter in the basal ganglia. In BPD, they found gray matter volume reduction in the anterior cingulate cortex and bilateral insula in BPD, a significant amount of this reduction in common with that of SZP (Ellison-Wright & Bullmore, 2010). These results reinforce the potential explanation for the reduction in mood regulation in the disorders. The function of the anterior cingulate cortex is generally the regulation of autonomic body functions, which raises some unique questions on whether BPD is also distinguished by a reduction in the ability to regulate functions such as heart rate and blood pressure.

Further studies (Amann et al., 2016) (Bora et al., 2012) reached similar conclusions, except that the distinctions were less obvious when the predominance of male patients was accounted for in the SZP studies. Amann et al. (2016) conducted a study with 45 patients with SAD, SZP, and BPD, to analyze how this third disorder could be compared with the other two neurologically with fMRI scans. They found that SAD and SZP displayed brain volume reduction in many corresponding regions, whereas individuals with bipolar disorder displayed no reduction in brain volume as compared to controls (Amann et al., 2016). Since the results for

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BPD were found to be different from the other two disorders as compared to the previously mentioned papers, there is still some lack of clarity about the cause of these disorders.

As these and other studies show, there are significant overlaps between the symptoms and neurological functioning of individuals with SZP, SAD, and BPD. Analyses find some of the same results, but there exist discrepancies in the brain regions that are found to be activated at different intensities. This data leads to the question of whether these disorders should be labelled as entirely distinct in the DSM. This question is important because categories of diagnosis lead to individualized treatment plans, and if studies find that the neurological cause of these disorders is similar, then the treatment for each of them should logically be similar as well.

Plan for thesis analysis

My research questions for this thesis are: At resting state, how are BPD, SZP, and SAD neurologically distinct in their functional connectivity? How does this compare to the differences between the psychosis biotypes? And how do covariates such as the usage of medication play a role in the observed neurological differences?

Functional connectivity refers to the amount of connections that each voxel has with the rest of the brain. High connectivity indicates high neurological functioning. fMRI scans can show how components of the brain are functionally connected in order to accomplish tasks, and this is observed by recording activation maps. This can be done with resting state images, and the variations in fMRI signaling indicates strength of connectivity (Rogers et al., 2007). By comparing the disorders and biotypes, a greater similarity in connectivity would be exhibited by fewer areas of the brain lit up.

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Although fMRI images of subjects completing cognitive tasks certainly have their benefits in conducting neurological research, resting-state images are equally important. An article by Shen (2015) explained that observing the functional connectivity of resting-state brains helps researchers understand how the brain works when it is just processing daily life. Certainly, individuals with various neurological disorders complete cognitive tasks with different parts of their brains, but at resting state, it is possible to see the ongoing neurological activity. As Shen expressed, “Scientists do hope to use resting-state connectivity to help improve treatments for neuropsychiatric patients who have already been diagnosed by other means” (Shen 2015). This is the reason why resting-state images were used for the research conducted in this thesis. By developing a better understanding of how the brain works at a resting state in individuals with these disorders, we can determine more comprehensively what is neurologically malfunctioning on a day-to-day basis and therefore develop a better treatment plan for these individuals.

In my thesis, I analyze fMRI images displaying the functional connectivity in individuals with SZP, BPD, and SAD, and in individuals with biotype 1, 2, and 3 of individuals who exhibit psychosis. This is part of a larger neurological study called the Bipolar Schizophrenia Network on Intermediate Phenotypes (B-SNIP), which includes biological characteristics in the comparison of neurological disorders. This inclusion allows for a more comprehensive understanding of these psychosis-related disorders. The three biotypes indicate the severity of psychosis, with psychosis defined as an inability to distinguish between reality and illusion. Symptoms of psychosis include delusions, hallucinations, incoherent or inappropriate behavior, and reduced socialization, motivation, and sleep. Biotype 1 includes the most severely impaired individuals, biotype 2 exhibits moderate symptoms, and biotype 3 displays more subdued symptoms. Previous studies have found that biotypes 1 and 2 display reduced gray matter

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throughout the cerebral cortex, whereas biotype 3 has reduced gray matter mostly in the regions responsible for emotion regulation (Asher, 2015).

I theorize that there is significant difference in brain functional connectivity between the three disorders, which leads to the belief that they should indeed be categorized as three distinct disorders in the DSM. I also compare the three biotypes of these disorders to determine whether there is a neurological difference between the three genetic categories, and I theorize that the three biotypes are indeed distinct. This in turn leads to the conclusion that each disorder requires its own unique treatment plan. In addition, I incorporate the usage of various types of medication into the study to determine whether the difference in brain connectivity is due to the use of medication or due to the presence of the disorder itself. Finally, I separate the subjects in the study based on the location of the fMRI scan in order to determine whether each of the cities diagnoses the disorder differently, and what impact this has on the brain connectivity found in the individuals found in that city. The locations for the fMRI scans were in Baltimore, Boston, Chicago, Dallas, Detroit, and Hartford.

Methods

Participants

1122 subjects from Baltimore, Boston, Chicago, Dallas, Detroit, and Hartford were recruited for this study. Participants had fMRI scans taken at a resting state. Both male and female subjects were formally diagnosed with the DSM-V with either BPD, SZP, and SAD. Their ages ranged between 15 and 65. Family members of the subjects with the

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aforementioned disorders were allowed to participate. To create control groups, individuals without any of the disorders were included and went through a screening process to ensure that they qualified as a suitable control.

Preprocessing

VNC Viewer was used to access the database of information. DPARSF (Data Processing Assistant for Resting-State fMRI) 4.4 Advanced Edition in DPABI (Data Processing & Analysis for (Resting-State) Brain Imaging) was the program used in MATLAB to preprocess the fMRI scans. This program has been found beneficial in previous research due to its ease of access (Chao-Gan & Yu-Feng, 2010). The first preprocessing stage was spatial normalization, followed by realignment, covariate regression, scrubbing, and distortion correction. The EPI functional images of each subject were overlaid on an MRI field map to look for artifacts, and the realign parameter was set to 3 mm to exclude subjects according to their maximum head motion.

The z score of each scan exhibits the standard deviation from the mean. To prevent the data from being skewed, 120 subjects with z scores above 2 were removed. Unfortunately, this resulted in all of the subjects from Boston to be removed during the preprocessing stages.

Non-parametric statistics were conducted with TFCE (Threshold-free Cluster Enhancement) Toolbox in MATLAB, with 1000 permutations. This calculated a t value, creating a null distribution. At the end of preprocessing, 629 subjects were available for use in the study, as the fMRI images of the remaining subjects were not smoothed and straightened enough to accurately compare with the images of other subjects. For the broad analysis of the subjects based on their DSM diagnosis and biotype, all 629 subjects were used.

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Categorization

For simplicity, links were made using WinSCP to the data folder containing the fMRI scans for each subject. Upon completion of the fMRI scans, an Excel spreadsheet was produced containing the covariates and other information including age, sex, framewise displacement, usage of antipsychotics, lithium, and mood regulators.

Initially, the subjects were divided in two separate studies by DSM diagnosis and biotype. Subjects with BPD, SZP, and SAD were placed in three respective groups of scans for the DSM study, and subjects with biotype 1, 2, and 3 were placed in three respective groups for the biotype study. Controls were included in both studies. After screening out subjects whose scans did not succeed in the preprocessing stages, there were 139 individuals with BPD, 104 with SAD, 158 with SZP, 103 with biotype 1, 137 with biotype 2, 161 with biotype 3, and 227 controls.

After dividing the subjects into their respective categories, additional comparisons were made with the covariates introduced above. The fMRI scans of individuals who took medication, for example, was compared with the mean of all the fMRI scans to determine the difference in activity for those who took medication. Of those comparisons, antipsychotics usage was the only covariate above found to be statistically significant for individuals who take this medication as opposed to those who do not.

The DSM and biotype categories were then compared with antipsychotic usage included as a covariate in an ANOVA analysis; no comparisons were statistically significant. Finally, subjects who took antipsychotics were examined to find brain regions which were activated more or less without considering DSM or biotype. The identified regions were then compared

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with subjects within each DSM and biotype categories without considering antipsychotic usage.

Analysis

In SPM12, a one-way ANOVA was used as a factorial design to compare the DSM disorders and the biotypes. Initially, site (Baltimore, Chicago, Dallas, Detroit, and Hartford), age, sex, and framewise displacement were used as covariates. Antipsychotic usage was later added as an additional covariate. In the factorial design of SPM12, variance was set to be unequal, and there was no grand mean scaling and no ANCOVA. Model estimation was set up with dependency on the model, and contrast manager was set up with dependency on model estimation. Residuals were not written in model estimation. In contrast manager, the t-contrasts for the DSM disorders were NC-BPD, NC-SAD, NC-SZP, BPD-SAD, BPD-SZP, and SAD-SZP. The t-contrasts for the biotypes were NC-1P, NC-2P, NC-3P, 1P-2P, 1P-3P, and 2P-3P. Both positive and negative contrasts were conducted in order to determine the comparisons in both directions for each contrast.

Other comparisons were conducted as well that were included in this study, using the subjects from the studies above. This was done in order to further determine whether the differences in brain connectivity for the individuals was due to their biotype or disorder, or whether it was due to the use of various types of medication or another reason. We compared individuals who took antidepressants with those who did not take antidepressants. This was done with a two-sample t-test. In the factorial design, 183 subjects were on antidepressants and 439 were not. A t-contrast was done between the two groups. The same set-up was done for subjects who took antipsychotics. 340 subjects took antipsychotics, whereas 282 did not. For a lithium

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study, 62 subjects were taking lithium and 560 were not. In a mood study, 190 subjects were on mood regulation medication whereas 432 were not.

A multiple regression model was used for several other comparisons. In a cognitive-sensorimotor study, we attempted to discern a significant difference in brain activity based on cognitive and sensorimotor functioning. This was conducted with 627 subjects. A t-contrast was done between the mean and cognitive results, and the mean and sensorimotor results. A PANSS (positive and negative syndrome scale) multiple regression was done with 397 subjects. Finally, a site regression model was set up, with 622 subjects in an f-contrast with a weights matrix of 4x9 to observe the main effect of site. Only in the sites regression were residuals produced in the model estimation, and another f-contrast was done with the residual data to determine any possible impact in site on the outcomes of the comparisons.

Due to the limited time to complete this research, age of onset was not considered as a covariate, so there was no analysis conducted on how the age of onset impacted the neurological data. A previous study (Tamminga et al., 2013) found that age of onset of these disorders had no impact on the categorization of the subjects, and another study (Clementz et al., 2016) did not include this covariate in their analysis of biotypes.

The ultimate goal of this thesis is to determine whether there are significant neurological distinctions between the DSM disorders and the biotypes. The additional comparisons were done in order to evaluate whether the neurological distinctions were due to the disorders themselves or to outside influences such as medications or the site at which the fMRI scans took place.

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Results

The neuronal connectivity of each of the biotypes and disorders was compared with each other and with the control group in order to determine the difference in what brain regions exhibited high connectivity. Table 1 displays the differences between all of the DSM disorders, Table 2 displays the regions of the biotypes, and Table 3 displays the differences of the additional covariates that we focused on. We compared the usage of antipsychotics, lithium, mood medication, and the PANSS scores to the mean in order to determine whether the differences in connectivity were due to the disorder itself or to the use of medication.

The second column in each table indicates the minimum voxel size needed for brain regions to be deemed significant. These values were determined through the `clustsimreport` function in Matlab, in order to determine the smallest number of voxels needed in a cluster in order to confirm that the brain activity was not due to chance (“AFNI Program”). The small voxel sizes exhibited in Table 3 were due to the lack of a need for this report because of the low number of any connectivity differences.

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Table 1: Significant brain regions in original study of comparison of DSM disorders. All comparisons include covariates of site, age, sex, and framewise displacement.

Comparison	Cluster size	Significant regions
Control – BPD	52	Medial frontal gyrus, anterior cingulate, precentral gyrus, postcentral gyrus, cingulate gyrus, superior temporal gyrus
BPD – Control	52	Superior frontal gyrus, uvula, declive
Control – SAD	30	Superior frontal gyrus
SAD – Control	30	No significance
Control – SZP	54	Postcentral gyrus
SZP – Control	54	Inferior parietal lobule, medial frontal gyrus, angular gyrus
BPD – SAD	42	Middle temporal gyrus, middle frontal gyrus, culmen, declive
SAD – BPD	42	No significance
BPD – SZP	34	Hippocampus, culmen
SZP – BPD	34	Anterior cingulate, cuneus
SAD – SZP	39	No significance
SZP – SAD	39	Supramarginal gyrus, inferior parietal lobule

Table 2: Significant brain regions in original study of comparison of biotypes. All comparisons include covariates of site, age, sex, and framewise displacement.

Comparison	Cluster size	Significant regions
Control – 1P	55	Superior temporal gyrus, postcentral gyrus, insula
1P – Control	55	Superior frontal gyrus, angular gyrus, precuneus
Control – 2P	42	Superior temporal gyrus
2P – Control	42	Superior frontal gyrus, middle frontal gyrus
Control – 3P	59	No significance
3P – Control	59	No significance
1P – 2P	30	No significance
2P – 1P	30	No significance
1P – 3P	22	No significance
3P – 1P	22	No significance
2P – 3P	30	Medial frontal gyrus
3P – 2P	30	No significance

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Table 3: Significant brain regions in each comparison of use of medication and of PANSS (Positive and Negative Syndrome Scale). All comparisons include covariates of site, age, sex, and framewise displacement.

Comparison	Cluster size	Significant regions
Antipsychotics – Mean	72	Paracentral lobule, lingual gyrus, putamen, cuneus, superior temporal gyrus
Mean – Antipsychotics	72	Superior frontal gyrus, supramarginal gyrus
Lithium – No Lithium	5	No significance
No Lithium – Lithium	5	No significance
Mood Medication – Mean	5	Putamen, insula
Mean – Mood Medication	5	Middle frontal gyrus, inferior occipital lobe, precentral gyrus
PANSS Positive – Mean	5	No significance
PANSS Negative – Mean	5	No significance
PANSS Total – Mean	5	No significance
PANSS Mean – Positive	5	Postcentral gyrus
PANSS Mean – Negative	5	Precentral gyrus
PANSS Mean – Total	5	Middle temporal gyrus, postcentral gyrus, supramarginal gyrus, insula, inferior parietal lobule

Table 4: All of the comparisons in the tables above are reorganized here to determine overlap in brain regions that exhibited greater connectivity.

Significant Regions	Comparisons	Total # Comparisons
Angular Gyrus	1P – Control, SZP – Control	2
Anterior Cingulate	Control – BPD, SZP – BPD	2
Cingulate Gyrus	Control – BPD	1
Culmen	BPD – SAD, BPD – SZP	2
Cuneus	SZP – BPD, Antipsychotic – Mean	2
Declive	BPD – Control, BPD – SAD	2
Hippocampus	BPD – SZP	1
Inferior Occipital Lobe	Mean – Mood Medication	1
Inferior Parietal Lobule	SZP – Control, SZP – SAD, PANSS Mean – Total	3
Insula	Control – 1P, Mood Medication – Mean, PANSS Mean – Total	3
Lingual Gyrus	Antipsychotics – Mean	1
Medial Frontal Gyrus	Control – BPD, SZP – Control, 2P – 3P	3

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Middle Frontal Gyrus	BPD – SAD, 2P – Control, Mean – Mood Medication	3
Middle Temporal Gyrus	BPD – SAD, PANSS Mean – Total	2
Paracentral Lobule	Antipsychotics – Mean	1
Precentral Gyrus	Control – BPD, Mean – Mood Medication, PANSS Mean - Negative	3
Precuneus	1P – Control	1
Postcentral Gyrus	Control – BPD, Control – SZP, Control – 1P, PANSS Mean – Positive, PANSS Mean – Total	5
Putamen	Antipsychotics – Mean, Mood Medication – Mean	2
Superior Frontal Gyrus	BPD – Control, Control – SAD, 1P – Control, 2P – Control, Mean – Antipsychotics	5
Superior Temporal Gyrus	Control – BPD, Control – 1P, Control – 2P, Antipsychotics – Mean	4
Supramarginal Gyrus	SZP – SAD, Mean – Antipsychotics, PANSS Mean – Total	3
Uvula	BPD – Control	1

The figures displayed below portray the brain regions that exhibited higher connectivity of the first group over the second. Other regions may have appeared as well, but the regions below are the largest. The comparisons found in each table that did not exhibit any significant regions are not included in the selection of images.

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Figure 1: Control – Bipolar Disorder. Sagittal, coronal, and transversal images are all oriented to exhibit the same (x, y, z) coordinates. The primary region that displayed greater connectivity in the control group is the superior temporal gyrus, shown here. Minimum cluster size to indicate significance is 52.

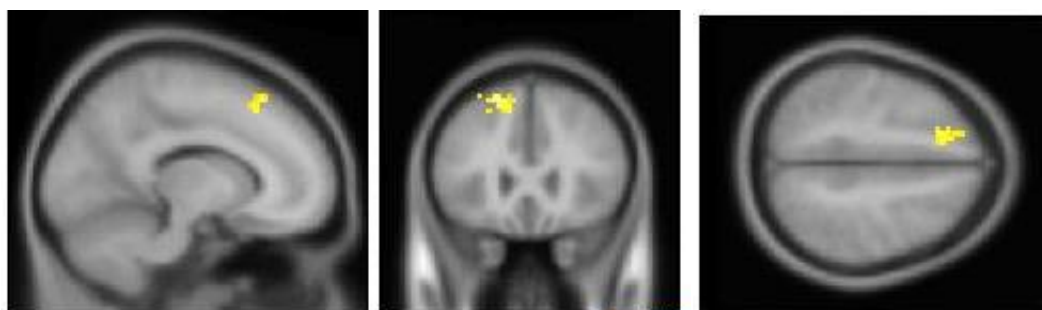


Figure 2: Bipolar Disorder – Control. Sagittal, coronal, and transversal images are all oriented to exhibit the same (x, y, z) coordinates. The primary region that displayed greater connectivity in BPD is the superior frontal gyrus. Minimum cluster size to indicate significance is 52.



Figure 3: Control – Schizoaffective Disorder. The region displayed here is the superior frontal gyrus. Minimum cluster size to indicate significance is 30.

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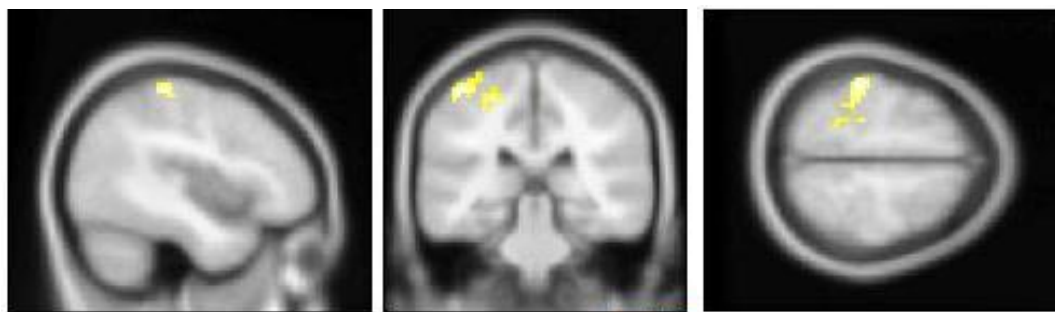


Figure 4: Control – Schizophrenia. The most significant region, displayed here, is the postcentral gyrus. Minimum cluster size is 54.



Figure 5: Schizophrenia – Control. The most significant region, displayed here, is the interior parietal lobule. Minimum cluster size is 54.

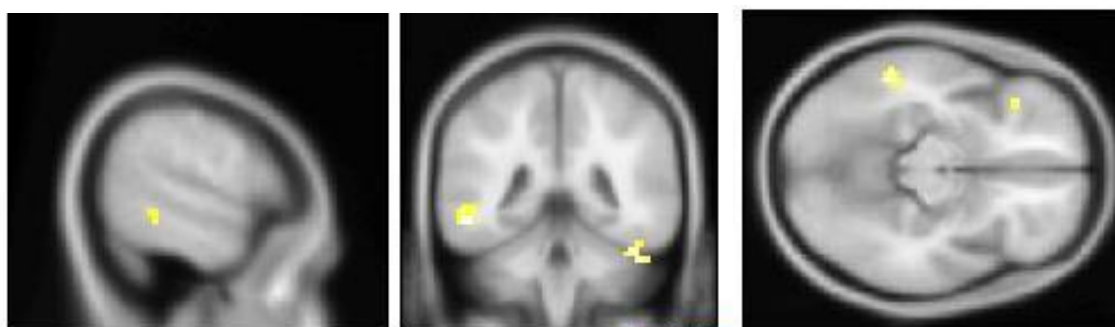


Figure 6: Bipolar Disorder – Schizoaffective Disorder. Middle temporal gyrus. Minimum cluster size is 42.

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Figure 7: Bipolar Disorder – Schizophrenia. The hippocampus is the most significant region with greater connectivity in BPD. Minimum cluster size is 34.

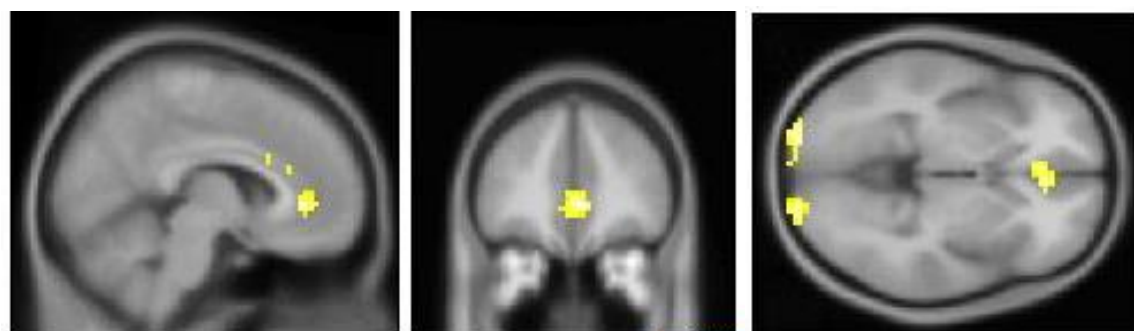


Figure 8: Schizophrenia – Bipolar Disorder. The region displayed here is the cuneus and anterior cingulate. Minimum cluster size is 34.

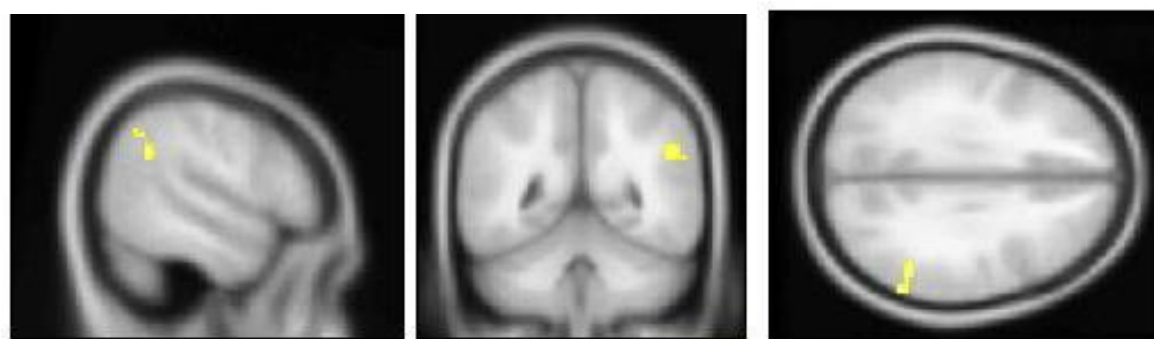


Figure 9: Schizophrenia – Schizoaffective Disorder. The region displayed here is the supramarginal gyrus. Minimum cluster size is 39.

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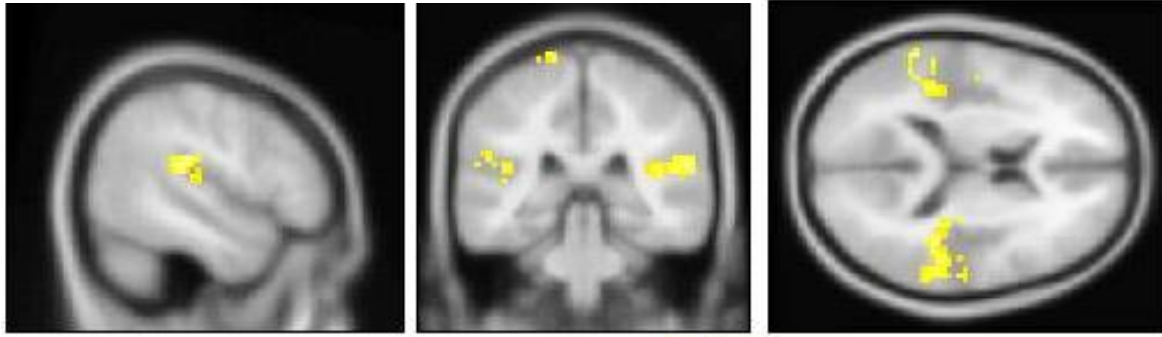


Figure 10: Control – 1P. The superior temporal gyrus exhibited greater connectivity in the control group. Minimum cluster size is 55.



Figure 11: 1P – Control. The region displayed here is the superior frontal gyrus. Minimum cluster size is 55.

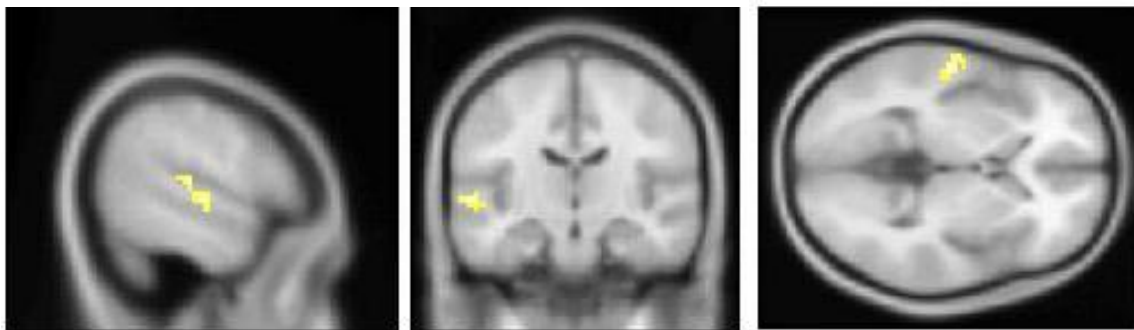


Figure 12: Control – 2P. The region here is the superior frontal gyrus. Minimum cluster size is 42.

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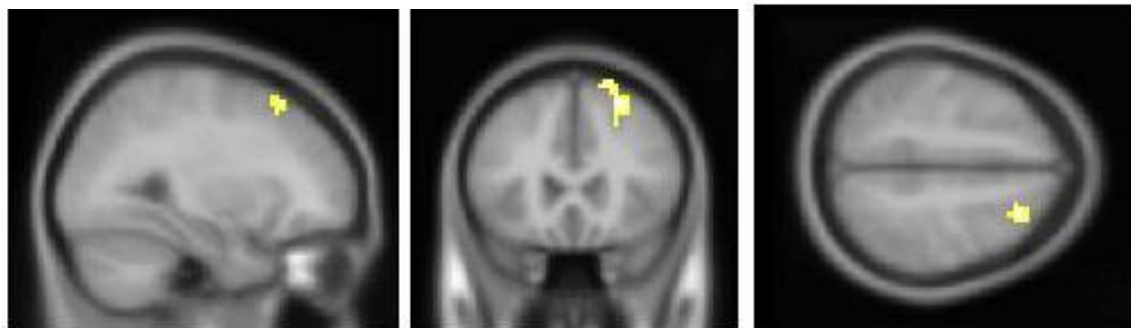


Figure 13: 2P – Control. The region displayed here is the middle frontal gyrus. Minimum cluster size is 42.

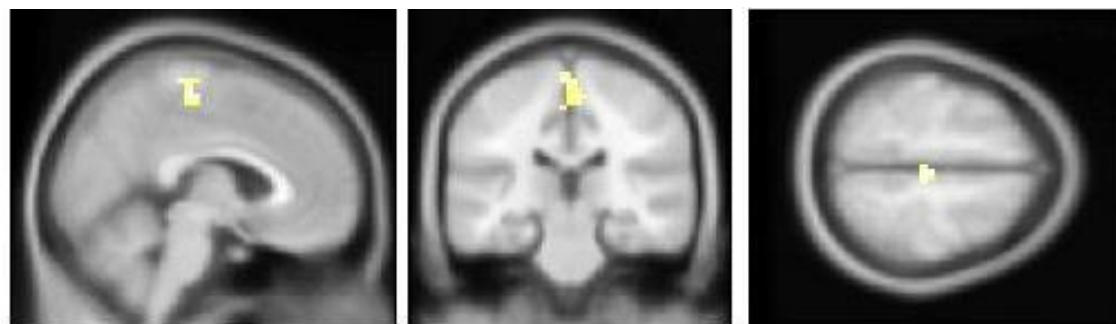


Figure 14: 2P – 3P. The region displayed here is the medial frontal gyrus. Minimum cluster size is 30.



Figure 15: Mean – Antipsychotics usage. The region with greater connectivity in the control group is the superior frontal gyrus. Minimum cluster size is 72.

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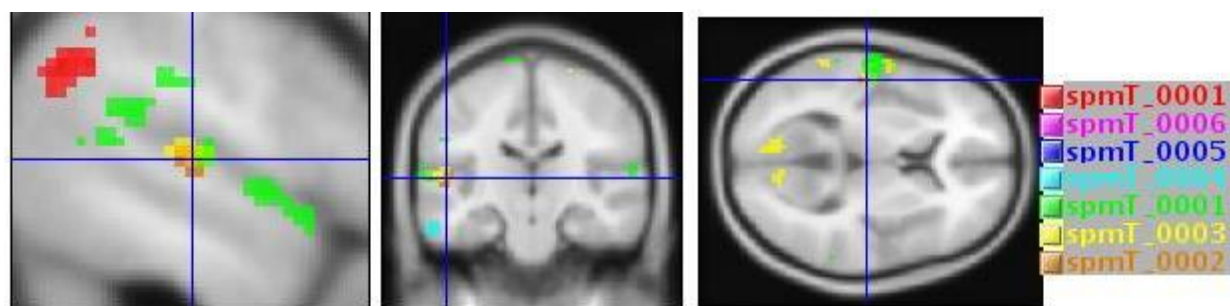


Figure 16: All DSM disorders (spmT_0001-0006, excluding 0002 in brown) overlaid with antipsychotic/no antipsychotic (spmT_0002) comparison. Sagittal, coronal, and transversal images are all oriented to exhibit the same (x, y, z) coordinates. The only significant region in common between the antipsychotic comparison and at least one disorder is the superior temporal gyrus. A cluster size of 30 was used.

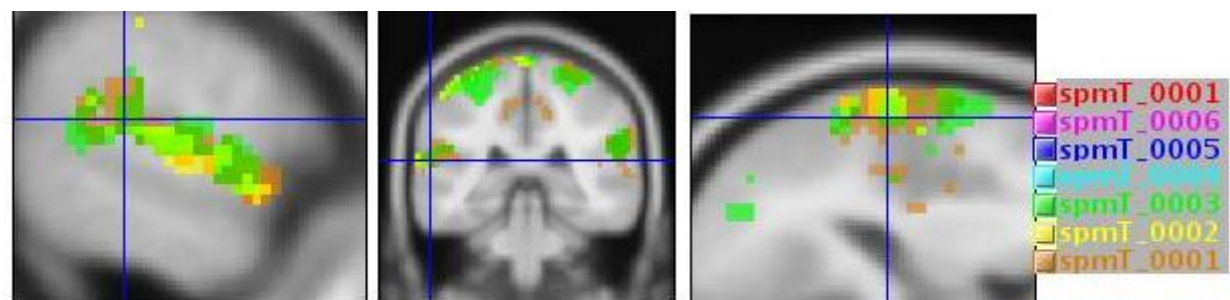


Figure 17: All biotypes (spmT_0001-0006, excluding 0001 in brown) overlaid with antipsychotic/no antipsychotic (spmT_0001 in brown) comparison. The only significant region in common between the antipsychotic comparison and at least one biotype is the superior temporal gyrus. A cluster size of 30 was used.

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Discussion

The initial study solely compared resting-state images displaying the connectivity between DSM disorders and biotypes in order to determine whether there is significant difference to deem each disorder and biotype as entirely distinct from one another. Resting-state images were used as opposed to images during cognitive tasks because this research prioritized gaining a better understanding of how the subjects' brains worked when no stimuli were introduced. By observing the resting state images, we can determine the ongoing neurological functions of each disorder and can attempt to discern what is malfunctioning in this ongoing daily functioning.

The selection of voxel size shown in all of the tables was done with a program called clustsimreport in Matlab in order to determine how large each cluster should be to remove all of the irrelevant noise. The program analyzes the amount of noise in each brain image and determines the minimum number of voxels required in a cluster to ensure that the functional connectivity is not due to chance ("AFNI Program").

Table 1 indicates the comparisons between the DSM disorders. The data in this table indicates there is a minor difference between the disorders, but this distinction is present nonetheless. The comparison with the greatest number of regions that exhibit greater connectivity is between BPD and the control group, with the control group having greater connectivity in the medial frontal gyrus, anterior cingulate, precentral gyrus, postcentral gyrus, cingulate gyrus, and superior temporal gyrus. BPD also exhibits greater connectivity than SAD in the middle temporal gyrus, middle frontal gyrus, culmen, and declive. Finally, BPD exhibits greater connectivity than SZP in the hippocampus, indicating the possibility of a greater ability

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to convert information to long term memory. The distinction between these disorders is subjective in whether it indicates that these disorders should be labelled as distinct, at least from a neurological perspective. There are not many brain regions that exhibit connectivity differences between the disorders.

When specifically looking at the comparisons with SAD in Table 1, there are no brain regions that exhibit greater levels of connectivity in SAD over the other groups. These results may indicate that individuals with SAD do not have any brain regions that are connected more strongly with the rest of the brain. In addition, when analyzing the regions that have greater connectivity in the other disorders over SAD, it is possible that those regions are caused by the covariates analyzed in Table 3. Control – SAD exhibits the superior frontal gyrus, but this region is also found to be more strongly linked to the rest of the brain in the mean group over the individuals who took antipsychotics in Table 3. BPD – SAD exhibits the middle temporal gyrus, middle frontal gyrus, culmen, and declive. However, the middle temporal gyrus was identified in the Mean – total PANSS comparison, and the middle frontal gyrus was identified to have greater connectivity in the mean group over individuals who took mood medication. SZP – SAD exhibits the supramarginal gyrus and inferior parietal lobule, but these regions are both found in the Mean – total PANSS comparison as well.

Since individuals with SAD can take a range of medications that frequently include both antipsychotics and mood medication (Cascade et al., 2009), and they also exhibit the positive and negative psychotic symptoms that are analyzed in the PANSS scale, these overlaps in brain regions are relevant. Perhaps the culmen and declive that we see has greater connectivity in BPD over SAD is significant to understand the actual neurological difference between these

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disorders, but these regions are not known for substantial cognitive functioning. Both regions are in the cerebellum, which is responsible for more autonomic functions.

Therefore, based on this perspective of the results in Tables 1 and 3, SAD is not neurologically distinct from BPD or SZP. This supports the notion that these three disorders should be set on a spectrum of psychosis disorders, rather than identifying SAD as an entirely unique disorder. BPD and SZP do show some differences between each other regarding their functional connectivity, so if these three disorders were set on a spectrum of psychosis disorders in the DSM, they could be put on opposite sides. BPD exhibits greater connectivity in the hippocampus and culmen, and SZP exhibits greater connectivity in the anterior cingulate and cuneus. The two disorders also exhibit substantial differences in brain connectivity when compared to the control group, indicating that there is indeed some unique functioning of these disorders as opposed to neurologically healthy individuals.

To finalize the analysis of the DSM disorders, Figure 16 displays all of the comparisons of BPD, SZP, and SAD and overlaid the images with the antipsychotics – mean comparison. The purpose of this analysis was to determine whether there was any brain region that any or all of the disorders overlapped with the use of antipsychotics, since the antipsychotics – mean comparison in Table 3 included many brain regions. The only region that was relevant was the superior temporal gyrus, as the antipsychotics – mean comparison overlapped with a few of the DSM comparisons at this region. The superior temporal gyrus has been found to be a significant region for schizophrenic individuals. SZP is frequently characterized by reduced P300 action potentials in the brain, and the reduction in these potentials is positively correlated with gray matter reductions in the left posterior superior temporal gyrus (McCarley, Shenton, & O'Donnell, 1993). Although the superior temporal gyrus is not implicated in any SZP

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comparisons in this thesis, there is still some relevant overlap with the other disorders, and BPD and SAD both exhibit some psychotic symptoms that are relevant to the research conducted by McCarley. Since the brain connectivity differences are so unique for each disorder, these results indicate that the use of antipsychotics does not impact all three disorders in the same way.

According to Table 2, there is no substantial difference between any of the biotypes. Biotypes 1 and 2 appear to be neurologically distinct from the control group, but Biotype 3 does not exhibit any difference. This portion of the results makes sense because Biotype 3 has the most subdued intensity of psychosis, so it is the closest to a neurologically healthy individual's behavior. When comparing the functional connectivity of Biotypes 1 and 2 to Biotype 3, there is no difference, which indicates that the mildest form of psychosis symptoms is not influenced by any detectable difference in brain functioning. These results are in agreement with a previous biotype study that found that Biotypes 1 and 2 differed significantly in their cognitive functioning when compared to the control group, but Biotype 3 exhibited no difference (Clementz et al., 2016).

The comparisons of Biotype 1 and 2 to the control group is similar as well. The superior temporal gyrus has greater connectivity in the control group as opposed to both biotype groups, and the superior frontal gyrus has greater connectivity in both of the biotype groups as opposed to the control. However, Control – 2P only exhibits the superior temporal gyrus, and 2P – Control only exhibits the superior frontal gyrus and middle frontal gyrus. For 1P, the biotype with the most severe psychosis symptoms, the control group also shows greater connectivity in the postcentral gyrus and insula, and 1P also exhibits greater connectivity in the angular gyrus and precuneus. This data indicates that when the psychosis symptoms become more severe, the amount of neurological differences from the control group increases.

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Figure 17, similar to Figure 16, displays all of the biotype comparisons overlaid with the antipsychotics – mean comparison. This analysis was done to determine whether the use of antipsychotics had any overall influence on all of the biotypes' neurological functioning. The image displays that the only main overlap was in the superior temporal gyrus, the same as Figure 16, but this overlap was not with every single one of the biotype comparisons. This is also relevant to the article by McCarley (1993), as a greater intensity of psychosis is likely correlated with a reduction in brain volume in the superior temporal gyrus and with the reduction in P300 potentials. These results indicate that the use of antipsychotics does not influence the neurological functioning of all of the biotypes in the same way.

Overall, the biotype data indicates that when the psychosis symptoms are more intense, there is some difference in brain functioning when compared to neurologically healthy individuals. However, since there is no difference between one biotype and another, these results are inconclusive. Further studies need to be conducted to further understand these differences in biotype characteristics.

Table 4 is provided as a method to see whether there are any brain regions that are implicated in the most comparisons of disorders, biotypes, or covariates. The superior frontal gyrus and superior temporal gyrus are involved in the most comparisons, with four and five comparisons, respectively. As it was previously expressed, the presence of these two regions in the biotype comparisons in Table 2 indicate a similar brain functioning in Biotypes 1 and 2. This data helps to provide the understanding that Biotype 1 exhibits some of the same functioning as Biotype 2, but also includes some additional brain functioning differences when compared to the control group. Besides the superior frontal gyrus and superior temporal gyrus, there are less than three comparisons that include each brain region, which indicates that although the neurological

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functioning of each disorder and biotype is only minimally different from each other, these differences are unique. Each disorder and biotype exhibits a unique neurological strength or deficiency that identifies it from the other disorders and biotypes.

Finally, the comparisons in Table 3 indicate some significant results that may be worth further analysis. The use of antipsychotics leads to an increase in functional connectivity in five brain regions, and contrastingly the lack of using antipsychotics causes an increase in connectivity in two other regions. Lithium intake does not impact functional connectivity, nor do any of the PANSS scales over the subjects who do not exhibit any PANSS symptoms. Mood medication does appear to impact functional connectivity, with two brain regions exhibiting greater connectivity in those who take this form of medication and three regions in those who do not. The PANSS Mean – total comparison exhibits a large number of brain regions that display greater connectivity, indicating that individuals who do not have positive or negative psychotic symptoms have a much greater amount of connectivity throughout the brain over those who do exhibit both forms of symptoms.

Conclusions

Given the vague results of some parts of this research, it is clear that more research must be conducted on the neurological implications of BPD, SZP, and SAD. BPD and SZP are certainly entirely distinct disorders, not only from a neurological perspective but from the list of symptoms of each disorder. BPD is more characterized as a mood disorder with the swings from manic to depressive states, whereas SZP is more characterized by hallucinations and delusions. Since the symptoms of SAD include some of those of the other two disorders, it makes sense that

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its neurological characteristics are undistinguishable from them. If these three disorders existed on a spectrum, as some researchers have previously considered, SAD should be between BPD and SZP.

Concerning the biotypes, it appears that intensity of psychosis symptoms, and the corresponding biotypes, is impacted by some distinctions in neurological functioning. When compared to the control groups, Biotype 1 has more neurological differences than Biotype 2, and Biotype 2 had more differences than Biotype 3. However, when comparing the biotypes to each other, there is no distinguishable difference in neurological functioning, so more research must be conducted to better determine whether there is indeed any impact that neurological functioning has on the intensity of psychosis.

In future studies, it will be necessary to include more subjects so there is a wider range of individuals to gather conclusions from. Previous studies have provided conflicting answers on this subject so the search for conclusive results must continue to better understand how to treat these disorders. In addition, including other covariates to better understand other possible reasons for the neurological differences will help gather more confident conclusions. As age of onset was not considered in this study, it will also be necessary to analyze whether this covariate has an impact on the neurological functioning. The age range of the subjects in this study was 15-65, but no comparisons of age groups was included.

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