ASSOCIATIONS BETWEEN ANTIPSYCHOTIC MEDICATIONS AND WHITE MATTER, COGNITION, OCULAR MOTOR VARIABLES, AND PSYCHOSIS SYMPTOMS

by

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(Under the Direction of Jennifer E. McDowell)

ABSTRACT

Certain antipsychotic medications, particularly clozapine, have been associated with a decrease in the differences in white matter, cognitive performance, and psychosis symptoms typical for individuals with psychosis syndromes. This project takes a multimodal approach to assessing these differences based on medication group via diffusion tensor imaging (DTI), the Brief Assessment of Cognition in Schizophrenia, saccade data, dosage, and symptom measures. This project included 984 participants from the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) consortium, and variables were assessed by medication group using ANOVAs and CCA. Results indicated similarities between participants taking clozapine and healthy individuals in white matter tracts related to aspects of cognition such as goal-oriented behavior and executive functioning. Similarities between these groups were also evident for some saccade tasks and cognitive performance. These results have clinical implications for psychiatric treatment strategies and may help elucidate some of the potential effects and benefits of clozapine.

INDEX WORDS: psychosis, clozapine, antipsychotic, diffusion tensor imaging (DTI), saccades, cognition

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DEDICATION

This thesis is dedicated to my late father, Kenneth Dumas, who always supported and believed in me. He encouraged me to chase my dreams no matter how big and inspired me to take steps to reach my full potential through exemplifying love for others and life, love for education, and perseverance. I would also like to dedicate this to my family, friends, and wonderful partner for all of their unconditional love and support throughout this process.

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INTRODUCTION

Antipsychotic drugs have been a crucial element of treatment for psychiatric conditions since the 1950s, however none have played as significant a role in the treatment of psychosis as clozapine (Khokhar et al., 2018). Clozapine did not initially command attention as an antipsychotic medication due to the lack of extrapyramidal side effects (e.g., muscle rigidity and tardive dyskinesia) which were seen as unfortunate but necessary features of all antipsychotic medications (Khokhar et al., 2018). As time progressed, some patients failed to respond to typical, or first generation, antipsychotic medications and clozapine was reintroduced as an atypical, or second-generation, antipsychotic (Khokhar et al., 2018). Despite the drug's efficacy, its use was drastically decreased in 1975 when eight patients on clozapine died of agranulocytosis, a condition characterized by low neutrophil levels resulting in an increased vulnerability to infection (Wagner et al., 2021). While this condition remains a valid cause for concern, advancements in medicine have resulted in a dramatic decrease in the risk of agranulocytosis and other dangerous side effects (Khokhar et al., 2018). With frequent monitoring of white blood cell counts, the risk of agranulocytosis has been reduced to 0.38% and consequently the potential benefits of clozapine may outweigh the risk of side effects for many psychosis patients (Khokhar et al., 2018). The drug's effects are widespread and previous research shows evidence of superior effectiveness in those with treatment resistant schizophrenia (Kane et al. 1988; Khokhar et al., 2018). Many of those who have received clozapine treatment experienced a significant improvement in their quality of life and the drug is still considered the most effective antipsychotic (Khokhar et al., 2018).

Individuals with psychosis may experience numerous symptoms that often cause great emotional and physical stress. These symptoms are typically divided into two categories: positive symptoms refer to those that exaggerate normal functions and perceptions and commonly include things like hallucinations and delusions, while negative symptoms are those that involve a decrease in normal functioning, such as lowered affect and anhedonia. Previous research determined that up to 80% of individuals with psychosis have depressive symptoms, and this is strongly associated with an increase risk for suicidal behavior (Khokhar et al., 2018). Some individuals with psychosis syndromes may experience mainly positive or negative symptoms, but many experience a combination (Andreasen et al., 1990). The primary goal of treatment plans for those with psychosis is symptom relief, typically through the administration of antipsychotic medications and various types of therapy. In studying potential treatments for these psychiatric conditions it is crucial to consider symptom management. To examine this, questionnaires are often used throughout studies to determine symptom course and whether the treatment being studied is providing relief.

One widely used questionnaire is the Positive and Negative Syndrome Scale (PANSS). This standardized scale is used to evaluate changes in symptomology over a treatment course and measures symptoms over the past week (Kay et al., 1987). Positive and negative symptoms are scored separately, and an overall scale is developed from these ratings (Kay et al., 1987). Past research has found associations between clozapine and improvements in positive and negative symptoms of psychosis (Wagner et al., 2021; Rosenheck et al., 1997). Wagner et al. (2021) conducted a meta-analysis to evaluate clozapine's efficacy as measured through positive, negative, and overall symptoms of schizophrenia. Results of this review were mixed, with some studies finding fewer hospitalizations and less severe positive and negative symptoms in those on

clozapine when compared with other medications (Wagner et al., 2021). In studies focusing on treatment-resistant schizophrenia, results were varied but some indicated that clozapine may be more effective than other medications in reducing overall and positive symptoms and mildly more effective than first generation antipsychotics (FGAs) in treating negative symptoms of psychosis (Wagner et al., 2021).

Positive and negative symptoms of psychosis have also been associated with differences in behavior and neurobiology evident through decreased cognitive performance and alterations in brain structure. Treatment with antipsychotics aims to alleviate at least most of these symptoms, yet often providers must prescribe drugs on a trial and error basis due to a lack of information about which drug is suited for each individual. Due to this, highly effective but underutilized drugs such as clozapine may become overlooked. Past studies have examined the relationship between clozapine treatment and variables such as brain structure, cognition, and symptoms in order to better determine which individuals would be best suited for this treatment and the benefits involved for those who receive it. There are many approaches to this type of study with one of the most popular being neuroimaging, specifically Magnetic Resonance Imaging (MRI).

MRI is used for gaining a deeper understanding of the neurological underpinnings of many psychiatric conditions, including psychosis syndromes. In the brain this type of imaging provides a highly detailed visual representation of white matter, gray matter, cerebrospinal fluid, and blood vessels, and can be used to evaluate both minor structural differences and larger physiological issues such as tumors, stroke, and inflammation. There are a variety of imaging protocols within the category of MRI that can be used for the evaluation of neuroanatomical differences, one of which is Diffusion Tensor Imaging (DTI).

DTI is an indirect method of evaluating the structural integrity of white matter using measurements of the diffusion of water molecules in the brain. The structural integrity of white matter may be disrupted by a variety of conditions such as Alzheimer's, neurodegenerative diseases, and psychosis syndromes, which in turn disrupts crucial functions such as communication between neural regions and cognition (Soares et al., 2013). White matter tissue microstructure differences (e.g. demyelination and poor axonal organization) may be examined using DTI metrics such as fractional anisotropy, or FA, and radial diffusivity, or RD (Fields, 2010; Soares et al., 2013). FA is a metric used to quantify the movement of water molecules in the primary vector along axonal lengths relative to the movement across axons, or the orthogonal vectors of water movement. This metric ranges from 0 to 1 with 0 indicating disorganized, or isotropic movement of water molecules, and 1 indicating organized anisotropic movement along the axon. Higher FA values indicate well organized white matter fibers with little disruption. Another metric frequently used is RD, which has an inverse relationship with FA and refers to the orthogonal vectors of water movement across axons. When FA values are closer to 1, RD values are typically lower, and vice versa. Higher RD values may indicate disruptions in white matter structure characterized by the disorganization of white matter fibers. FA and RD are often used in conjunction due to their differing sensitivity to white matter disruptions. FA is likely more sensitive to overall changes in white matter microstructure, while RD is likely more sensitive to specific microstructural changes, such as demyelination (Tae et al., 2018).

Research has established that significant differences in white matter structure exist in those with psychosis compared to healthy controls, primarily in the context of compromised structural integrity (Luo et al., 2020). Individuals with psychosis were found to have decreased FA values when compared to individuals without psychosis in many regions such as the

cingulum, fornix, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus (Luo et al., 2020; Skudlarski et al., 2013). These white matter tracts are associated with functions of cognitive performance such as executive control, verbal memory, visuospatial memory, language processing, and goal-oriented behavior and are thought to be affected by treatment with antipsychotic medications (Connor et al., 2018; Luo et al., 2020; Raslau et al., 2015). Previous research found that individuals on some antipsychotics showed improvement in areas of white matter deficits after treatment, most markedly in areas related to cognition (Luo et al., 2020). Luo et al. (2020) found that those on risperidone showed more improvement in FA values and cognitive performance thanother drugs, but acknowledged that individuals on clozapine had more initial impairment and potentially less effective medication treatment (indicated by scores on the Brief Assessment of Cognition, the PANSS, and lower chlorpromazine equivalents).

General cognitive performance in psychosis can be evaluated in a multitude of ways including traditional cognitive testing and other behavioral methods such as saccadic eye movement analysis. Past research indicates that those with psychosis experience disruptions in cognition when compared to healthy individuals, in terms of both general cognitive performance and functions such as inhibitory control (Gotra et al., 2020). This can lead to negative impacts on impulse and emotional control, social functioning, employment, and the ability to live independently (Gotra et al., 2020; Keefe et al., 2006). General cognitive performance in those with psychosis has been assessed through the use of the Brief Assessment of Cognition in Schizophrenia, or BACS (Keefe, 2004). The BACS is a cognitive test consisting of six subtests that assesses the features of cognition thought to be most strongly negatively impacted by schizophrenia such as verbal and working memory, motor speed, executive functioning,

attention, information processing, and verbal fluency (Keefe et al., 2004). Research has found that those with psychosis consistently score significantly lower on these tests of cognition than those without psychosis, and these deficits may be affected by antipsychotic medication treatment (Cheuk et al., 2024; Hill et al., 2010; Keefe et al., 2004).

Other aspects of cognition such as the inhibition can be assessed through the collection of ocular motor data. Analysis of ocular motor variables often considers two main types of saccades: reflexive, which are eye movements made towards a peripheral stimulus typically referred to as prosaccades, and volitional, which are more complex and require higher level cognitive functions such as inhibition, decision making, and spatial memory (McDowell et al., 2011). Volitional saccades are often measured through antisaccade tasks which involve inhibiting one's instinct to look towards a peripheral stimulus and instead looking at the mirror image location. Individuals with psychosis tend to perform similarly to healthy individuals on prosaccade tasks in terms of correct reaction times and percent of trials performed correctly, indicating that the neural circuitry involved in these reflexive responses may be largely unaffected by psychosis syndromes (McDowell et al., 2011). Conversely, those with psychosis demonstrate significant differences compared to healthy individuals in error rates, correct reaction times, and accuracy on tasks requiring some aspects of cognition, such as the antisaccade task (McDowell et al., 2011; Reilly et al., 2014). This difference in performance is not thought to be due to a lack of understanding of the task since those with psychosis perform error correction similarly to healthy individuals, but may instead be due to differences in the additional neural circuitry required to perform these tasks (McDowell et al., 2011). The prosaccade and antisaccade tasks may be used in conjunction, with the prosaccade task serving

as a baseline measure of performance. Antipsychotics may impact performance as measured by metrics such as error rate and correct reaction time (Reilly et al., 2008). Previous literature does not offer consistent conclusions on this, but some studies posit that antipsychotics, particularly second generation antipsychotics (SGAs), are associated with reduced latencies and error rates on antisaccade tasks (McDowell et al., 2011). As a result of this, more research is warranted to gain a comprehensive view on the association between antipsychotics and saccades through the comparison of both FGAs and SGAs as well as individual drugs such as clozapine.

An important consideration when conducting analyses on medication data is the effects of dosage. If dosage is not accounted for in analyses, it is possible that any differences found between groups may in fact be due to participants receiving a higher or lower dose of medication rather than due to legitimate biological/behavioral differences between groups. As various antipsychotic medications are most effective at different doses, it is crucial to compare dosage information in standard units. Using a method such as a calculated chlorpromazine (CPZ) equivalent allows for comparisons between individual medications and combinations of antipsychotics through a comprehensive measure of dosage (Andreasen et al., 2010).

The Andreasen method is an established way of calculating CPZ equivalence developed with the intention of providing a method of measuring cumulative lifetime exposure to antipsychotic medications (Andreasen et al., 2010). This method is based on the “Expert Consensus Guideline Series. Optimizing Pharmacologic Treatment of Psychotic Disorders” which encompasses data from 47 experts in the United States asked to recommend doses of various antipsychotics that they considered equivalent to a predetermined dosage range of haloperidol or risperidone (Kane et al., 2003). Using the results of this study, Andreasen et al.

(2010) performed linear regression and power transformations to develop formulas for each drug which were then used to determine their equivalence to 100 mg of chlorpromazine and 2 mg of haloperidol. These equivalents were then entered into a dose-year formula and used to determine cumulative lifetime exposure to antipsychotic medications (Andreasen et al., 2010).

Data for the current study were collected through the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) consortium. The B-SNIP consortium is a multi-site research group that has identified three biologically distinct (regardless of DSM diagnosis) groups of individuals with psychosis (Clementz et al., 2022). The group's goal is to develop more biologically based ways to inform treatment of psychosis disorders, promote objective, optimized treatment, and inform psychiatric care for those with psychosis (Clementz et al. 2022).

The current study aims to evaluate the clinical, behavioral, and cognitive differences in those with psychosis specific to medication status. This was accomplished by analyzing DTI metrics FA and RD, cognitive performance as measured by the BACS, correct reaction times of pro and antisaccades, the percent of antisaccades performed correctly, dosage measured by CPZ equivalence, and positive and negative symptoms measured by PANSS scores. Participant groups included those purely on clozapine (no other antipsychotics or mood stabilizers; n = 31), a non-pure clozapine group (clozapine combined with other antipsychotic drugs and/or mood stabilizers; n = 38), those on FGAs; n = 42, those on SGAs excluding clozapine; n = 432, and a healthy control group; n = 441. The current hypotheses were that individuals on clozapine would show fewer differences from participants without psychosis in FA and RD when compared to other medication groups, participants on clozapine would have similar reaction times to healthy individuals on correct saccade trials, particularly correct antisaccades, and faster reaction times

than other medication groups as well as similar percent correct on antisaccade trials when compared to healthy participants, and a higher percent correct when compared to other medication groups. It is hypothesized that those on clozapine will also exhibit lower symptom scores on the PANSS than other groups, particularly for positive symptoms, and will demonstrate BACS scores more similar to healthy participants than other medication groups.

METHODS

Participants

The following methods were as described in Kelly et al. (2021) and Tamminga et al. (2013) using data from both the B-SNIP consortium and the second iteration of this study (B-SNIP 2). Data included consists of that collected at 2 sites of the original B-SNIP consortium, Baltimore and Hartford, and all 5 sites of the B-SNIP 2 consortium: Boston, Chicago, Dallas, Georgia, and Hartford. Participants included 543 individuals with psychosis and 441 healthy participants ranging from ages 15-63 years (see **Table 1**) and all signed written informed consent statements approved by appropriate review boards. To qualify for the study, all individuals were required to achieve a standardized score of at least 60 on the Wide Range Achievement Test (WRAT-IV) Word Reading subtest. Healthy participants were identified as free of a current axis I disorder via the nonpatient version of the Structured Clinical Interview for DSM-IV (SCID). Participants with psychosis underwent diagnosis confirmation of schizophrenia, schizoaffective disorder, or bipolar I disorder with psychosis through the administration of the SCID by qualified clinical raters. General cognitive performance was evaluated using the BACS (Keefe et al., 2004). Symptom severity and current psychosis status were assessed through the administration of the PANSS, the Montgomery-Asberg Depression Rating Scale (MADRS), Barratt Impulsiveness Scale 11, Birchwood Social Functioning Scale, Young Mania Rating Scale (YMRS), and Schizo-Bipolar Scale (Birchwood et al.,1990; Kay et al., 1987; Keshavan et al., 2011; Montgomery & Asberg, 1979; Patton et al., 1995; Young et al., 2000). In addition to diagnostic and cognitive testing, participants underwent urine toxicology screening for illegal substances and were free of known neurological illnesses (Kelly et al., 2021).

Procedures

Diffusion Weighted Imaging

Image acquisition for both projects was conducted on 3T scanners but specific parameters differed by project and procedures are as follows. B-SNIP 1 parameters were as described in Skudlarski et al. (2010). Images were collected at two sites, Baltimore and Hartford, using echo planar imaging slice sequences with a diffusion-weighted protocol. Full scan parameters by site are outlined in **Table 2**. B-SNIP 2 images were collected at 5 locations, Boston, Chicago, Dallas, Georgia, and Hartford also using echo planar imaging slice sequences with a diffusion-weighted protocol. During the course of the project Boston and Georgia underwent hardware/software upgrades so data are considered to be from 7 separate sites. Full scan parameters for B-SNIP 2 by site can be found in **Table 3**.

DTI data were processed according to Brown et al. (2021) and Berardi et al. (2024). Raw data files were converted to NIFTI format from PAR/REC and DICOM and checked for image quality. Volumes showing motion artifacts were removed and scans, b-value, and b-vector tables were adjusted accordingly. Data were then preprocessed using FMRIB Software Library (FSL; Smith et al., 2006). Images were registered to the first non-weighted (b=0) image using affine transformation after being corrected for eddy current-induced distortions. The Brain Extraction Tool was used to remove non-brain tissue and FSL's Diffusion Toolbox was used to create single images for FA and RD for each subject before fitting a tensor to each white matter voxel.

Tract-Based Spatial Statistics (TBSS) was used to analyze all FA images (Smith et al., 2006). To begin, all subjects' FA images were registered into standard space (MNI152) and a mean FA image for the sample was calculated. This image was then used to produce an FA skeleton consisting of the core of common fiber bundles before using a combination of three

masks to restrict voxels to those containing 18 major white matter tracts (Schaeffer et al., 2015). The first mask applied selected voxels with an FA value greater than 0.2 (See **Figure 1a-1d)**. The next mask selected voxels with a >5% probability of belonging to each tract used from the Johns Hopkins University tractography atlas, and the final mask selected voxels from each scan that belonged to the sample FA skeleton. The voxels that remained after masking were used for analysis and mean FA and RD values were calculated for each tract for each subject.

As described in Berardi et al. (2024), data were harmonized using ComBat, a tool commonly used in small sample size gene expression analysis, to attempt to remove inter-site variability and parameter-related variation in FA and RD metrics (Fortin et al., 2017, Johnson et al., 2007). The harmonization process began with standardization of the means and variances of both FA and RD values as recommended by Johnson et al. (2007) and a location (mean) and scale (variance) adjustment model (Fortin et al., 2017). ComBat was then utilized to develop parameter estimates and stabilize variances using an Empirical Bayes framework (Fortin et al., 2017, Johnson et al., 2007). Healthy individuals' FA and RD values were then used to calculate harmonized FA and RD values to preserve variance due to natural psychosis-related differences and attempt to eliminate site effects as well as parameter-related variation. The formula used for the calculation of harmonized FA and RD values is depicted in **Figure 2**.

As data from the two projects were collected using different parameters, appropriate strategies to combine data were used. Because parameter differences may result in issues in later steps of TBSS that seek to create a mean FA skeleton from the means of all subjects' FA images, projects were run separately through TBSS steps 1, 2, and 3. These steps involved calculating the registration of images into MNI152 space and the application of this transformation to each subject's FA image. After this, harmonization was performed on the transformed images using

ComBat. Harmonization attempts to remove variance due to differing parameters and scanners in the process of removing site differences, so projects were only combined in TBSS post harmonization to attempt to address the issue of parameter differences. To confirm successful harmonization, one-way ANOVAS were run on FA and RD values by site for each tract post harmonization and these results revealed no significant group differences. TBSS was then completed and masking steps performed to obtain final FA and RD values.

Saccade Data

Saccade data collection procedures are as outlined in Huang et al. (2022). Eye movement data were collected through the use of an infrared light source and SR Research Ltd.'s EyeLink II, a head-mounted video-based eye tracker used for recording pupil position (sampling rate of 500 Hz; Neurobehavioral Systems Inc.). Trial stimuli were presented in a darkened room on 22 inch CRT monitors and participants placed their chin on a chin rest for the duration of the tasks. In both studies prosaccade and antisaccade tasks were presented, in that order. Examples of these tasks are included in **Figure 3.** Both tasks used peripheral stimuli presented at +/- 10° and 15° locations relative to a central fixation cross and inter-trial intervals ranged from 1500-2500 ms.

The prosaccade task consisted of 3 blocks of 32 trials with each block using a different fixation condition, and both B-SNIP 1 and B-SNIP 2 collected data for all three fixation conditions. The fixation conditions were "gap," "synchronous," and "overlap." In the "gap" condition, the central fixation point (a red cross) was extinguished 200 ms before the peripheral stimulus, a white circle, appeared. In the "synchronous" condition, the peripheral stimulus appeared at the same time as the central fixation point was extinguished, and in the "overlap" condition, the peripheral stimulus and the fixation point were both visible for 200 ms before the fixation point was extinguished. All conditions began with the participant fixating on the central

point and they were instructed to shift their gaze as quickly as possible to the peripheral stimulus when it appeared. Counterbalancing of trial types was accomplished by varying the order of peripheral stimulus locations and fixation conditions. Breaks were given between blocks in which participants were to close their eyes to avoid fatigue, but not move from the chinrest.

The antisaccade task consisted of 4 blocks of 20 trials for each fixation condition with the same breaks between blocks as in the prosaccade task. B-SNIP 1 only collected trials with the "overlap" fixation condition while "gap" and "overlap" conditions were collected in B-SNIP 2. The timing of the fixation conditions was identical to the prosaccade task. The antisaccade task began with the same fixation cross and used the same peripheral stimulus location as the prosaccade task, but used a white square as the stimulus. Trials were counterbalanced by varying the order of the stimulus presentation location. Before the task, participants were instructed not to look at the square and instead, look at the mirror image location of the stimulus.

Data were scored using MATLAB (The MathWorks Inc., Natick, Massachusetts). Trials were scored for direction, later translated to correctness, and latency and excluded for reasons such as anticipatory responses (saccades made before 90 ms post stimulus presentation), no movement during the trial, or blinks during stimulus onset. After scoring, data underwent quality control and averages were created using SAS software, Version 9.4 of the SAS system for Linux. Copyright © 2016 SAS Institute Inc., Cary, NC, USA.

Medication Data

Participants with psychosis were grouped by their antipsychotic medication status and participant numbers by group are included in **Table 1.** Chlorpromazine (CPZ) equivalent antipsychotic average daily dose was calculated using the Andreasen (2010) method and participants were grouped into 3 dosage categories based on distributions and tertiles. Values up

to 213 mg were considered a low dose, 213 mg to 469 mg was categorized as a medium dose, and 469 mg and above was categorized as a high dose.

Statistical Analyses

Preliminary analyses were conducted on all variables prior to final analyses. One-way ANOVAS were run to determine differences between medication groups for all three prosaccade timing conditions for correct reaction times, antisaccade overlap correct reaction times and percent correct, the composite score and the subtest scores for the BACS, positive and negative PANSS scores, CPZ equivalence, and DTI variables (FA and RD) for each of the 18 tracts. The composite BACS score was calculated using the scores of individuals without psychosis on the six subtests and corrected for age and gender according to Keefe et al. (2008).

A canonical correlation analysis (CCA) was run to assess the relationship between white matter structural variables (FA and RD for each tract) and behavioral variables (prosaccade overlap reaction times, antisaccade overlap reaction times and percent correct, and BACS composite scores). Significant components were analyzed further using ANOVAs to explore relationships between white matter, behavioral variables, and medication group.

To explore the relationship between white matter, behavioral variables, and antipsychotic medication dosage, ANOVAS were run using the significant components resulting from the CCA as dependent variables and CPZ equivalence category (low, medium, high) as the independent variable.

RESULTS

Preliminary Analyses

Saccade Metrics

Before running the final analyses combining variables of interest, preliminary analyses were run on each of the variables individually to assess differences by medication group. First, preliminary analyses of saccade reaction times and percentage of correct antisaccade overlap trials by medication group were conducted using several one-way analyses of variance (ANOVAs). Significant between groups differences were evaluated using Bonferroni post hoc analyses and descriptive statistics and results are contained in **Tables 4** and **5** and **Figure 4**. Results of the ANOVAs revealed that there was no significant difference in correct reaction times by medication group for the prosaccade gap condition ($F(4, 833) = 1.48$, $p = .206$), however there were significant between groups differences for the prosaccade sync condition ($F(4, 854) = 4.58$, $p = .001$) and overlap condition ($F(4, 849) = 3.31$, $p = .011$). There were also significant differences by medication group for antisaccade overlap correct reaction times ($F(4,834) = 6.66$, $p < .001$), and percent correct ($F(4, 835) = 34.22$, $p < .001$).

BACS

After conducting preliminary analyses on saccade variables, one-way ANOVAs were conducted on the BACS composite scores and each of the 6 BACS subtests by medication group. Between groups differences were found in the BACS composite *z*-score, $F(4, 959) = 70.29$, $p < .001$. When data were analyzed by subtest, results showed that there were significant differences by group for verbal memory ($F(4, 958) = 38.33$, $p < .001$), digit sequencing ($F(4,959) = 30.33$, $p < .001$), symbol coding ($F(4, 958) = 66.57$, $p < .001$), and the Tower of London ($F(4, 959) =$

19.33, $p < .001$) *z*-scores, but no significant differences for the token motor task ($F(4, 955) = 1.62$, $p = .167$) or the verbal fluency task ($F(4, 956) = .19$, $p = .945$) *z*-scores. Bonferroni post hoc analyses were conducted to determine specific group differences and group comparisons are shown in **Table 6**.

Symptom Measures

One-way ANOVAs were also conducted on PANSS positive and negative total scores by medication group. Healthy participants were not included in this analysis as they were not administered the PANSS. Results for the analysis of positive symptom scores showed minorly significant between groups differences. which were evaluated using an LSD post hoc test. No significant between groups differences were found for negative symptom total scores and the results of both ANOVAs are included in **Table 7**. Due to the minorly significant group differences for positive symptom total scores and the lack of significant group differences for negative symptom total scores, PANSS scores were not included in further analyses.

DTI Variables

DTI metrics (FA and RD) were also evaluated to explore any potential differences in white matter structural integrity by medication group using ANOVAs (See **Table 8**). All 18 tracts initially showed significant between groups differences for FA, but after Bonferroni post hoc analysis only 15 tracts showed significant differences between medication groups. These include the left and right anterior thalamic radiation (ATR), left cingulum cingulate gyrus portion (CGC), left and right cingulate gyrus - hippocampal portion (CGH), forceps major, forceps minor, left and right inferior fronto-occipital fasciculus (IFOF), left and right inferior longitudinal fasciculus (ILF), left and right superior longitudinal fasciculus (SLF), and left and right uncinate fasciculus (UF). Results of ANOVAs performed on RD values by medication

group revealed that there were significant between groups differences for 8 tracts, and 6 of these showed significant differences after Bonferroni post hoc analyses. Tracts with significant differences in RD by medication group included the left ATR, left and right CGH, forceps major, and left and right ILF. Specific differences by medication group for FA and RD are shown in **Table 9** and examples of some of the tracts displaying medication group differences are depicted in **Figure 5.**

Analysis of Structure and Cognition

In order to examine the relationship between white matter and behavioral variables, a canonical correlation analysis (CCA) was run using the DTI metrics FA and RD for all 18 tracts as well as behavioral variables consisting of prosaccade and antisaccade overlap correct reaction times, antisaccade overlap percent correct, and BACS composite scores. These behavioral metrics were selected to probe the relationship between performance on more reflexive tasks, such as the prosaccade task, and variables that are strongly related to several aspects cognitive performance, such as antisaccade task measures and the BACS composite score. The results of this analysis revealed two significant components. For the first significant component the first set, DTI variables, received the most weight from FA values and the second set, behavioral variables, of the first component received the most positive weight from the variables that most strongly measure cognitive performance, antisaccade percent correct and the BACS scores. There were also strong negative weights from prosaccade overlap and antisaccade overlap correct reaction times in the behavioral set, indicating lower values for these variables in this association. **Tables 10** and **11** contain the canonical loadings for set 1 and 2 of component 1. The second significant component resulting from the CCA received the most weight from RD values for the first set of variables and all four variables in the second set were negatively weighted with

the BACS composite scores showing the strongest weight. Canonical loadings for both sets of the second component are contained in **Tables 12** and **13.**

Follow-up Analyses

Structure and Cognition by Medication Group

One-way ANOVAs were conducted to explore the relationship between the CCA output variables for component 1 and medication group. A scatterplot of sets 1 and 2 for component 1 is depicted in **Figure 6.** Results of the first ANOVA revealed significant differences between medication groups for set 1 (mainly represented by FA values), $F(4, 788) = 8.85$, $p < .001$. Healthy individuals had significantly higher values for this set than those on SGAs ($p < .001$) and those in the non-pure clozapine group ($p < .001$) but did not significantly differ from those on FGAs ($p = 1.000$) or those in the pure clozapine group ($p = .775$). Those in the non-pure clozapine group also displayed significantly lower values than those on FGAs ($p = .039$) and SGAs ($p = .012$). The results of the ANOVA examining set 2 of component 1 by medication group revealed significant differences as well, $F(4, 788) = 11.68$, $p < .001$. For this set of variables, healthy individuals demonstrated significantly higher values than those on SGAs ($p < .001$) and those in the non-pure clozapine group ($p < .001$). Those on SGAs also had significantly higher values than in the non-pure clozapine group ($p = .035$).

The relationship between set variables for component 2 and medication group was also explored using ANOVAs. A scatterplot of sets 1 and 2 for component 2 is shown in **Figure 7.** There were significant differences between medication groups for set 1 (mainly representing RD values), $F(4, 788) = 10.04$, $p < .001$. For this set healthy individuals had significantly lower values than those on FGAs ($p = .007$), SGAs ($p < .001$), and those in the non-pure clozapine group ($p = .001$) but did not significantly differ from the pure clozapine group, $p = 1.000$. Set 2

(representing behavioral variables) also showed significant differences between groups, $F(4, 788) = 49.46$, $p < .001$. For this set of variables healthy individuals showed significantly lower values than all other groups ($p < .001$ for all comparisons).

Structure and Cognition by Dosage

One-way ANOVAs were also run to examine the potential association between both sets of the first significant CCA component and dosage as measured by CPZ equivalence. A scatterplot of the component 1 variable sets by dosage group is included in **Figure 8.** Significant differences by medication group were found for set 1 of component 1, $F(4, 788) = 5.96$, $p = .003$. For this set representing FA values, individuals in the high dosage group showed significantly lower values than those in the low ($p = .023$) and medium dosage groups ($p = .004$). There were no significant differences by group for set 2 of component 1, $F(4, 788) = 2.47$, $p = .087$. There were also no significant differences by group for set 1 ($F(4, 788) = 0.11$, $p = .900$) or set 2 ($F(4, 788) = 0.41$, $p = .661$) of component 2. A scatterplot of the component 2 variable sets by dosage group is included in **Figure 9.**

DISCUSSION

The current project evaluated neurobiological, behavioral, and cognitive differences in individuals with psychosis and how these relate to medication treatment received as well as dosage. This evaluation was carried out through the use of white matter structural variables (FA and RD), behavioral variables including pro and antisaccade reaction times, percent of antisaccades performed correctly, the BACS composite score, symptoms measured by positive and negative PANSS scores, and dosage as measured by CPZ equivalence. Preliminary results revealed that there were significant differences by medication group for several of the variables analyzed, and these differences remained apparent throughout follow-up analyses conducted.

Results of preliminary saccade analyses align with previous findings by McDowell et al. (2011) that those with psychosis show disruptions in saccade performance that may be affected by treatment with antipsychotic medications. For prosaccades, medication group differences in correct reaction time found in only the synchronous and overlap conditions suggest that potential differences may be seen better in more cognitively complex prosaccade tasks, which supports previous research on timing conditions of saccade tasks (McDowell et al., 2011). Findings from the analysis of antisaccade overlap correct reaction times indicate that clozapine treatment may benefit those aspects of cognition impaired in psychosis syndromes such as inhibition, decision making, and spatial memory. While the pure and non-pure clozapine groups did not demonstrate antisaccade correct reaction times significantly different from other medication groups, a key aspect of this is that the two clozapine groups were the only groups that showed no significant differences compared to healthy individuals. This indicates that there may be an association between clozapine treatment and improved saccade performance, which supports previous

findings that clozapine may be beneficial in treating cognitive performance deficits associated with psychosis. Specifically, this aligns with findings from McGurk (1999), who conducted a meta-analysis evaluating the effects of clozapine on cognition and concluded that clozapine may help improve the deficits in psychomotor speed typically associated with psychosis syndromes. Results from the analysis of the percent of antisaccades performed correctly broadly support previous findings from McDowell et al. (2011) which stated that those with psychosis perform a significantly lower percentage of antisaccades correctly when compared to healthy individuals.

Conclusions drawn from analyses of BACS composite scores support previous research demonstrating that individuals without psychosis typically perform better than those with psychosis on tests of general cognitive performance (Keefe et al., 2004). Medication group differences evident in analyses of individual BACS subtests suggest that differences in cognition associated with medication treatment could be related to more specific aspects of cognition. Two subtests supported the more general conclusion by Keefe et al. (2004) that those without psychosis perform significantly better than those with psychosis. These two subtests are verbal memory and symbol coding, which measure processing speed, executive functioning, and attention. These two tests do not reveal group differences beyond that which is shown by a composite score, but results of the digit sequencing and TOL subsections may provide insight into more specific potential group differences. The digit sequencing subtest, which primarily measures short term and working memory, shows differences in performance compared to healthy individuals for all groups except those purely on clozapine and similar results were found for the TOL subtest, which primarily evaluates executive functioning, planning, and problem solving. These outcomes suggest an association between normalized performance in tasks measuring these aspects of cognition and clozapine treatment. Previous literature shows mixed

support for these findings, with some studies citing limited or no improvement in executive functioning and working memory with clozapine treatment and many citing improvement in overall measures of cognitive performance (McGurk, 1999).

In terms of symptoms - both positive and negative - the lack of significant differences in PANSS scores between groups adds to the mixed results of studies examining the associations between clozapine and symptoms of psychosis syndromes. As Wagner et al. (2021) described in their meta-review of the efficacy of clozapine in treating psychosis syndromes, analyses of clozapine's effect on positive and negative symptoms of psychosis have produced conflicting results. Some studies in this analysis indicate that clozapine may be associated with less severe symptoms, however others indicate that there is no significant difference between those who are treated with clozapine and those who are not (Wagner et al., 2021). These inconsistencies in the results of studies evaluating the associations between clozapine and symptoms of psychosis syndromes may indicate that other methods of assessment could be more informative and effective in determining potential differences in symptoms based on medication status.

When considering the analysis of FA and RD by tract, it is evident that medication group shows potential associations with white matter integrity. Overall, FA values exhibited more differences between groups by tract than RD values, with 11 of the 15 significant tracts showing that the only medication group with FA values not significantly lower than healthy individuals' was the pure clozapine group. These tracts are the ATR bilaterally, the left CGC, the forceps major and minor, IFOF bilaterally, ILF bilaterally, left SLF, and left UF, and are primarily associated with functions such as spatial learning and memory, executive functioning, emotional processing, behavior regulation, social functioning, goal-oriented behavior, semantic processing, object recognition, visually-guided behaviors, working memory, and attention.

Examples of these tracts are shown in **Figure 5**. The pure clozapine group showed minimal differences from other medication groups with FA being higher for this group than FGAs in the left ATR, which is associated with executive functioning, and right CGC (associated with emotional regulation) and higher than the non-pure clozapine group in the left CGC and forceps major and minor (associated with occipital lobe communication and executive function/motor control, respectively). These results suggest that while pure clozapine is not associated with significantly higher FA values compared to most other medication groups, the values are more similar to those of healthy individuals than any other medication group examined and indicate a level of white matter structural integrity comparable to that of individuals without psychosis. These results support previous findings that clozapine treatment may be associated with increased FA values compared to pre-clozapine treatment values, especially in the ILF, UF, ATR, SLF, IFOF, and cingulate bundle (Ozcelik-Eroglu et al., 2014). Considering RD values, 6 tracts showed significant differences by medication group and the non-pure clozapine group exhibited significantly higher values compared to healthy individuals in the left ATR, indicating more disrupted white matter structure. Those purely on clozapine had similar RD values compared to healthy individuals in all tracts, though other medication groups had similar results, which indicates that the lack of difference in RD values may not be unique to clozapine treatment.

Results of the canonical correlation analysis (CCA) revealed two components showing significant relationships between structural variables (FA and RD for all 18 tracts) and behavioral variables (saccade variables and BACS composite scores). The first significant component (see **Tables 10** & **11**) indicates a positive association between white matter structural integrity as measured by FA values and behavioral variables strongly representing cognitive

performance (antisaccade percent correct and the BACS composite scores), suggesting that as white matter integrity increases in this sample, so does cognitive performance. Specifically, higher FA values are associated with higher antisaccade overlap percent correct, higher BACS composite scores, and lower reaction times for correct pro and antisaccade overlap trials. These findings echo previous literature that shows a positive correlation between FA values and cognitive performance (Faria et al., 2019). The second significant component output by the CCA (see **Tables 12** & **13**) indicates a relationship between RD values and behavioral variables. As the set 2 (behavioral) loadings for this component are negative this suggests that as RD values increase for this sample, participants exhibit lower BACS composite scores, a lower percentage of antisaccade overlap trials performed correctly, and faster reaction times for correct pro and antisaccade overlap trials. Component loadings for the behavioral variable set are strongest for the BACS composite score, lower for the percent of correct antisaccade trials and lowest for saccade reaction times, indicating that the majority of the variance for this set of the component is explained by the variable most strongly representing overall cognitive performance (BACS composite score).

Further exploration of CCA results through ANOVAs allowed for the evaluation of significant components by medication group. Using the first CCA component which primarily represented FA values, faster saccade task reaction times, higher antisaccade percent correct and higher BACS composite scores, ANOVAs revealed FA values similar to healthy for those in the pure clozapine group and those on FGAs, which supports previous findings by Ozcelik-Eroglu et al. (2014) but does not support findings indicating a lack of improvement in white matter structural integrity in those on FGAs (Chen & Nasrallah, 2019; Sagarwala & Nasrallah, 2021). Set 2 results show a similar pattern that aligns partially with findings by Haddad et al. (2023), as

the pure clozapine and FGA groups showed similar behavioral variable values representing cognitive performance compared to healthy.

The second set of ANOVAs which included set variables from component 2 of the CCA, revealed that for set 1 (structural variables mainly representing RD), only those in the pure clozapine group showed similar RD values compared to healthy individuals, which supports the theory that clozapine may be associated with fewer white matter integrity deficits compared to other antipsychotic medications (Chen & Nasrallah, 2019; Sagarwala & Nasrallah, 2021). The ANOVA results for set 2, mainly represented by BACS composite scores, supported previous findings and preliminary analyses in that healthy individuals performed significantly better than all other groups (Gotra et al., 2020).

Analyses of component output variables by dosage revealed that for component 1, individuals in the high dosage category based on CPZ equivalence had lower means for the set representing FA values (set 1) than individuals in the medium and low dosage categories. The difference found in FA values by dosage may be in part due to the severity of symptoms requiring a higher dosage of medication for effective treatment, and this is supported by previous findings by Waszczuk et al. (2022) which show that structural integrity of white matter may be more compromised in those with more severe psychosis symptoms or increasing disease progression. The lack of differences in set 2 of component 1 and both sets of component 2 reveal that there may be no significant association between dosage and RD values or behavioral variables and indicate that differences found in these variables are likely not due to dosage.

Information gained from these analyses partially supports the hypotheses outlined previously. Preliminary analyses of DTI metrics in several of the tracts analyzed support the hypothesis that those on clozapine would show fewer differences from healthy individuals than

other medication groups. Hypotheses concerning saccade performance were partially supported, with participants in the pure clozapine group demonstrating similar reaction times to healthy for the prosaccade sync and overlap conditions as well as the antisaccade overlap condition. However, the hypothesis that participants on clozapine would demonstrate faster reaction times for correct saccades than those in other medication groups was not supported for any task tested, nor was the hypothesis that participants on clozapine would perform similarly to healthy individuals and better than other medication groups in terms of the percent of antisaccades performed correctly. Analyses of positive and negative PANSS scores did not support the hypothesis that those on clozapine would exhibit lower symptom scores than other medication groups, and there was mixed support for the hypothesis that BACS scores for those on clozapine would be similar to healthy. Analyses of composite BACS scores did not support this hypothesis, however it was supported by the results of analyses of the digit sequencing and TOL subtests.

No research is without limitations, and while this study provides valuable contributions to the field's knowledge of the associations between clozapine and the neurobiological, behavioral, and cognitive aspects of psychosis, there are some necessary considerations. First, comparing groups of vastly different sample sizes is not ideal, however the sample used for this study was not epidemiological, so groups were not predefined. Future research should aim to maintain more even group sizes for optimal statistical power and accuracy and reliability of results. Next, other factors contributing to differences in study variables should be considered, such as the influence of socioeconomic status (and in turn access to healthcare, quality education, housing, etc.) on white matter integrity and cognitive performance. These factors have potential influence and should be incorporated, however this project provides a solid foundation for investigating differences associated with antipsychotic medications using a multimodal approach.

Main findings in this project reinforce that the type of antipsychotic one is treated with may be associated with differences in neurobiology, behavior, and cognitive performance. Results of the analysis of DTI variables reveal that those treated with clozapine display similar white matter structural integrity to healthy individuals in areas associated with functions such as executive and social functioning, behavior regulation, goal-oriented behavior, and working memory. These functions are crucial for everyday activities such as engaging in relationships with others, maintaining employment and housing, and successfully navigating one's environment. Consequently, there could be an association between clozapine treatment and one's ability to carry out these daily tasks, though more research is necessary before reaching this conclusion. Cognitive performance was shown to be significantly related to both medication group and white matter structure through the analysis of multiple types of variables, which provides a more robust foundation for drawing conclusions about these associations. Those in the pure clozapine group were shown to have similar values for behavioral variables in the analysis of a CCA component representing FA values and behavioral variables mainly representing cognitive performance, providing further support for the theory that clozapine may have some benefit to cognitive performance as it relates to functions like inhibition and memory.

The current project employed a multimodal approach to evaluating the association between antipsychotic medications, in particular clozapine, and white matter integrity, behavioral variables as assessed by cognition testing and saccade metrics, and psychosis symptoms. The results of this project have clinical implications in that they provide a biological approach to evaluating potential effects of antipsychotic medications, which may add valuable insights into the benefits of certain types of medications and in turn help minimize the trial and error of treatment that many patients must endure in their provider's attempt to identify an

effective medication. As previously stated, clozapine is effective but highly underutilized, and increasing available information about potential benefits may help provide support for its consideration in treatment plans. Patient prioritization is crucial, especially for vulnerable populations such as those with psychiatric conditions. Many individuals with psychosis experience hardships such as job loss, food and housing insecurity, and loss of relationships in addition to the devastating symptoms of psychosis. Consequently, enduring the trial and error method of finding the correct medication, often with more errors than successes, can result in patients becoming frustrated with the lack of symptom relief, side effects, the costs of filling prescriptions, and other factors inherent to this method of treatment selection. After enduring this, many patients are unwilling to try a new medication if they do manage to find one that provides some relief or begin to refuse treatment altogether. Developing ways to better identify effective medications and providing a more empirical basis for treatment promotes a streamlined approach to psychiatric care and this project's multimodal approach adds to existing literature that helps provide a comprehensive biological approach to care for individuals with psychosis.

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Table 1. Demographics of the Sample by Medication Group

	1st Generation (n = 42)	2nd Generation (n = 432)	Clozapine (Pure) (n = 31)	Clozapine (Non pure) (n = 38)	Healthy Controls (n = 441)
Age (yrs): M(sd)	40.7(12.4)	36.6(12.2)	34.9(10.7)	38.2(11.5)	37.0(12.0)
Sex (% Female)	59.5%	47.7%	41.9%	44.7%	56.7%
Ethnicity (% Hispanic)	16.6%	12.3%	12.9%	10.5%	11.8%
Race (% Black)	57.1%	41.0%	19.4%	23.7%	31.7%
Race (% White)	33.3%	47.9%	61.3%	65.8%	51.9%
Race (% Multiracial/Other)	9.6%	11.1%	19.3%	10.5%	16.4%

Table 2. Scan Parameters by Site for B-SNIP 1

Parameters (DTI, EPI)	**Site**	
	Baltimore	Hartford
Magnet	Siemens TrioTim	Siemens Allegra
Head coil (channels)	8	8
TR (ms)	6,700	6,300
TE (ms)	92	85
Flip angle (°)	90	90
FOV (mm)	1610 x 1610	1540 x 1540
Acquisition matrix	128 x 128	128 x 128
Slice Thickness (mm)	3	3
Voxel Size (mm)	1.8 x 1.8 x 1.8	1.72 x 1.72 x 3
No. of Slices	48	45
Slice Orientation	axial	axial
No. of Directions	30	32
No. of *b*=0 images	1	1

Table 3. Scan Parameters by Site for B-SNIP 2

Parameters (DTI, EPI)	**Site**						
	Boston (2015-16)	Boston (2017-20)	Chicago	Dallas	Georgia (2015-19)	Georgia (2019-20)	Hartford
Magnet	GE Signa HDxt	GE Discovery MR750	Philips Achieva	Philips Achieva	GE Signa HDxt	GE Discovery MR750	Siemens Skyra
Head coil (channels)	8	32	32	8	8	32	32
TR (ms)	11,350	10,000	10,000	10,000	10,000	10,000	10,000
TE (ms)	min	min	min	min	min	82.7	min
Flip angle (°)	90	90	90	90	90	90	90
FOV (mm)	256 x 256	310 x 310	256 x 256	256 x 256	256 x 256	307 x 307	256 x 256
Acquisition matrix	128 x 128	128 x 128	128 x 128	128 x 128	128 x 128	128 x 128	128 x 128
Slice Thickness (mm)	2	2.4	2	2	2.4	2.4	2.4
Voxel Size (mm)	2 x 2 x 2	2.4 x2.4 x 2.4	2 x 2 x 2	2x2x2	2.4 x 2.4 x 2.4	2.4 x 2.4 x 2.4	2 x 2 x 2
No. of Slices	73	73	73	73	61	72	73
Slice Orientation	axial	axial	axial	axial	axial	axial	axial
No. of Directions	64	64	64	64	64	64	64
No. of *b*=0 images	1	7	7	7	7	7	7

Tables 4, 5. Descriptive Statistics and ANOVA Results of Saccade Variables. Table 4 contains means and standard deviations of saccade variable analyses. Table 5 depicts significant medication group differences by saccade metric.

Reaction Times in Milliseconds: m(SD)					**% Correct: m(SD)**
Group	**Pro Gap:**	**Pro Sync:**	**Pro Over:**	**Anti Over:**	**Anti Over:**
1st Generation	157.9(25.8)	183.8(30.7)	210.7(50.3)	405.3(90.7)	57.7(23.8)
2nd Generation	163.9(35.0)	190.8(35.4)	214.6(48.8)	385.9(83.9)	62.2(24.0)
Pure Clozapine	164.2(32.9)	189.6(35.1)	222.6(48.8)	353.7(72.6)	56.1(24.5)
Non-pure Clozapine	175.7(36.3)	203.0(38.5)	237.1(61.6)	392.8(104.2)	45.4(26.0)
Healthy	163.0(27.8)	183.2(28.9)	209.1(40.8)	362.3(66.1)	76.88(19.1)

Variable	***p***
Pro Sync Correct Reaction Time	
HC < SGA **HC < Non-pure Clozapine**	.016 .009
Pro Overlap Correct Reaction Time	
HC < Non-pure Clozapine	.009
Anti Overlap Correct Reaction Time	
HC < FGA **HC < SGA**	.022 <.001
Overlap Percent Correct	<.001
HC > FGA **HC > SGA** **HC > Pure Clozapine** **HC > Non-pure Clozapine** **SGA > Non-pure Clozapine**	<.001 <.001 <.001 <.001 <.001

Table 6. Significant Medication Group Differences by BACS Composite and Subtest

Variable	***p***
Composite Score	
HC > FGA	<.001
HC > SGA	<.001
HC > Pure Clozapine	<.001
HC > Non-pure Clozapine	<.001
Verbal Memory & Symbol Coding	
HC > FGA	<.001
HC > SGA	<.001
HC > Pure Clozapine	<.001
HC > Non-pure Clozapine	<.001
Digit Sequencing	
HC > FGA	<.001
HC > SGA	<.001
HC >Non-pure Clozapine	<.001
Tower of London	
HC < FGA	<.001
HC < SGA	<.001

Table 7. Results of ANOVAs for Positive and Negative Symptom Scores by Group

Variable	***F*(df)**	***p***
Positive Symptom Scores	2.69(3, 503)	.046
FGA > SGA **FGA > Pure Clozapine** **FGA > Non-pure Clozapine**		.039 .022 .012
Negative Symptom Scores	2.06(3, 503)	.105

Table 8. Tracts with Significant Medication Group Differences for FA and RD

		Left		Right	
Tract	**Metric**	***F*(df)**	***p***	***F*(df)**	***p***
Anterior Thalamic Radiation	**FA** **RD**	9.29(4, 979) 4.32(4, 979)	<.001 .002	7.61(4, 979)	<.001
Cingulum-Cingulate Gyrus Portion	**FA**	7.15(4, 979)	<.001		
Cingulate Gyrus-Hippocampal Portion	**FA** **RD**	4.59(4, 979) 4.62(4, 979)	.001 .001	3.26(4, 979) 5.88(4, 979)	.011 <.001
Inferior Fronto-Occipital Fasciculus	**FA**	10.96(4, 979)	<.001	8.89(4, 979)	<.001
Inferior Longitudinal Fasciculus	**FA** **RD**	12.18(4, 979) 2.83(4, 979)	<.001 .024	6.97(4, 979) 3.72(4, 979)	<.001 .005
Superior Longitudinal Fasciculus	**FA**	5.96(4, 979)	<.001	5.03(4, 979)	<.001
Uncinate Fasciculus	**FA**	6.71(4, 979)	<.001	5.57(4, 979)	<.001
Bilateral Tracts					
Forceps Major	**FA** **RD**	17.24(4, 979) 8.42(4, 979)	<.001 <.001	N/A	N/A
Forceps Minor	**FA**	12.73(4, 979)	<.001	N/A	N/A

Table 9. ANOVA Results of Significant Medication Group Differences by Tract.

Group Comparison	Tract (FA)	*p*	Group Comparison	Tract (FA)	*p*
Healthy > FGA	ATR (L)	< .001	**Pure Clozapine > FGA**	ATR (R)	.034
	ATR (R)	< .001		CGC (L)	.023
	CGC (L)	.006	**SGA > FGA**	ATR (L)	.042
	Forceps Major	.004		ATR (R)	.023
	Forceps Minor	.002	**SGA > Non-pure Clozapine**	ATR (L)	.033
	IFOF (L)	.001		Forceps Major	.019
	IFOF (R)	.005		Forceps Minor	.018
	ILF (L)	.002	**Pure Clozapine > Non-pure Clozapine**	CGC (L)	.026
	ILF (R)	.050		Forceps Major	.012
	SLF (L)	.010		Forceps Minor	.040
	UF (L)	.004			
	UF (R)	.027			
Healthy > SGA	ATR (L)	.010	**Group Comparison**	**Tract (RD)**	***p***
	ATR (R)	.017			
	CGC (L)	.011	**FGA > Healthy**	Forceps Major	.021
	CGH (L)	.003			
	CGH (R)	.009			
	Forceps Major	< .001			
	Forceps Minor	< .001			
	IFOF (L)	< .001			
	IFOF (R)	< .001			
	ILF (L)	< .001	**Non-pure Clozapine> Healthy**	ATR (L)	.028
	ILF (R)	.001			
	SLF (L)	.007			
	SLF (R)	.031			
	UF (L)	.017			
Healthy > Non-pure Clozapine	ATR (L)	< .001	**SGA > Healthy**	CGH (L)	< .001
	ATR (R)	.023		CGH (R)	< .001
	CGC (L)	.009		Forceps Major	< .001
	Forceps Major	< .001		ILF (L)	.046
	Forceps Minor	< .001		ILF (R)	.006
	IFOF (L)	< .001			
	IFOF (R)	< .001			
	ILF (L)	< .001			
	ILF (R)	.002			
	SLF (L)	.042			
	UF (L)	.004			
	UF (R)	.004			

Tables 10, 11. Canonical Loadings for Component 1, Sets 1 and 2. Table 10 shows canonical loadings for set 1 of component 1 of the results of a CCA, and Table 11 shows canonical loadings for set 2 of component 1. The weights range from -1 to 1, with positive values closer to 0 being highlighted in light red and values closer to 1 being highlighted in darker shades of red. Negative values closer to 0 are shown in light blue, while values closer to -1 are shown in dark blue. Set 1 for component 1 primarily represents mean FA values for all tracts and Set 2 primarily represents antisaccade overlap percent correct and the BACS composite scores.

Variable (Component 1, Set 1)	**Weight**
Left Inferior Fronto-Occipital Fasciculus (FA)	.615
Right Inferior Fronto-Occipital Fasciculus (FA)	.595
Forceps Minor (FA)	.590
Forceps Major (FA)	.571
Left Uncinate Fasciculus (FA)	.558
Right Uncinate Fasciculus (FA)	.496
Left Anterior Thalamic Radiation (FA)	.495
Left Corticospinal Tract (FA)	.488
Left Anterior Thalamic Radiation (RD)	-.582
Right Superior Longitudinal Fasciculus (RD)	-.597

Variable (Component 1, Set 2)	**Weight**
AS Over Percent Correct	.376
BACS Composite	.366
AS Over Correct RT	-.782
PS Over Correct RT	-.837

Tables 12, 13. Canonical Loadings for Component 2, Sets 1 and 2. Table 12 shows canonical loadings for set 1 of component 2 of the results of a CCA, and Table 13 shows canonical loadings for set 2 of component 2. Set 1 for component 2 primarily represents mean RD values for all tracts and Set 2 primarily represents the BACS composite score.

Variable (Component 2, Set 1)	**Weight**
Forceps Major (FA)	-.399
Right Cingulate Gyrus - Hippocampal Portion (FA)	-.415
Left Anterior Thalamic Radiation (FA)	-.493
Forceps Major (RD)	.337
Left Inferior Longitudinal Fasciculus (RD)	.272
Left Inferior Fronto-Occipital Fasciculus (RD)	.195
Left Superior Longitudinal Fasciculus (RD)	.175
Left Anterior Thalamic Radiation (RD)	.136
Right Cingulate Gyrus - Hippocampal Portion (RD)	.129
Left Uncinate Fasciculus (RD)	.111

Variable (Component 2, Set 2)	**Weight**
AS Over Correct RT	-.039
PS Over Correct RT	-.238
AS Over Percent Correct	-.437
BACS Composite	-.914

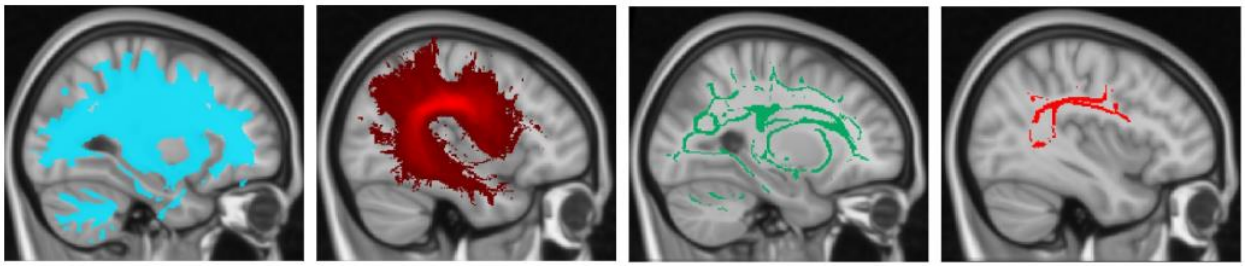


Figure 1a **Figure 1b** **Figure 1c** **Figure 1d**

Figures 1a-1d. Depiction of masking steps used in TBSS processing. Three masking steps are used to eliminate white matter fibers that do not meet certain criteria before calculating the final FA and RD means for each tract for each subject. **Figure 1a** depicts the first masking step, which thresholds FA values at 0.2 and removes anything below this value. **Figure 1b** shows the second masking step which uses tract probability masks from the Johns Hopkins University White Matter Tractography Atlas to create a mask for each subject keeping only voxels that have a >5% probability of belonging to a given mask. The third masking step (**Figure 1c)** shows the overlap between voxels in individual subjects' scans and the mean FA skeleton. The fourth image depicts selected voxels from each scan that met the FA threshold of 0.2, had a probability of belonging to the selected tract >5%, and overlapped with the voxels shared by all subjects (FA skeleton) (**Figure 1d).**

$$y_{ijv}^{\text{ComBat}} = \frac{y_{ijv} - \widehat{\alpha}_v - f\left(\mathbf{X}_{ij}, \widehat{\boldsymbol{\beta}}_v\right) - \gamma_{iv}^*}{\delta_{iv}^*} + \widehat{\alpha}_v + f\left(\mathbf{X}_{ij}, \widehat{\boldsymbol{\beta}}_v\right)$$

Figure 2. Formula for ComBat Harmonization of FA and RD. Fortin et al. (2017) describes the variables in the formula as follows: "Let y_{ijv} represent the [DTI metric (FA, RD)] for voxel *v* for scan *j* at site *i*, ... α_v is the overall [DTI metric] measure for voxel *v*, **X** is the n x K design matrix for the K covariates of interest (e.g., gender, age), *f* is a prespecified multivariate function of the covariates outlined by $\boldsymbol{\beta}_v$. We assume that the form of *f* is the same for all voxels, and that $\boldsymbol{\beta}_v$ is sufficient to capture all voxel-specific effects. The terms γ_{iv} and δ_{iv} represent the additive and multiplicative site effects of site *i* for voxel *v*, respectively… the nonlinear component $f(\mathbf{X}_{ij}, \boldsymbol{\beta}_v)$... [is modeled by using] cubic splines. Cubic splines are composed of piecewise third-order polynomials with control points (knots) specified in advance. They allow to model nonlinear relationships between two variables in a flexible and smooth fashion".

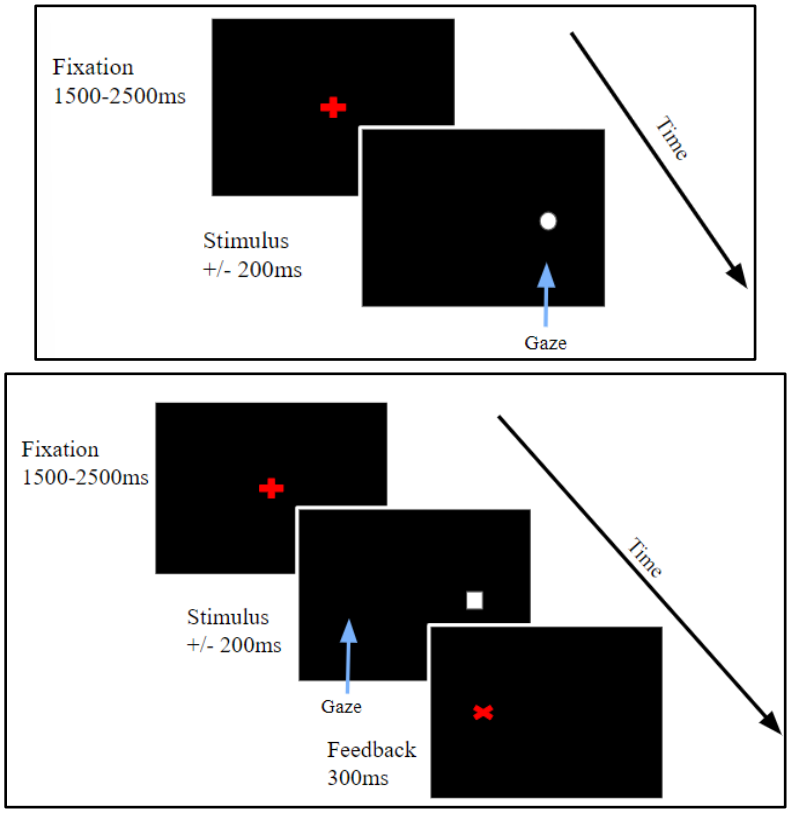


Figure 3. Examples of Prosaccade and Antisaccade Tasks. The top image shows the prosaccade task. The subject was instructed to look at the central fixation cross, and when the white circle appeared, look at it. In the prosaccade task the fixation cross was extinguished 200ms before (gap condition), at precisely the same time (synchronous condition), or 200ms after stimulus onset (overlap condition) depending on the timing condition being presented. The antisaccade task is depicted in the bottom image. For this task, participants were to gaze at the central fixation cross and when the white square appeared, look at the same location on the opposite side. A red X then appeared to provide feedback to the participant and show them where they should have looked during the trial. In this task the fixation cross was extinguished either 200ms after (gap condition) or before stimulus onset (overlap condition). Inter-trial intervals for both tasks ranged from 1500-2500 ms.

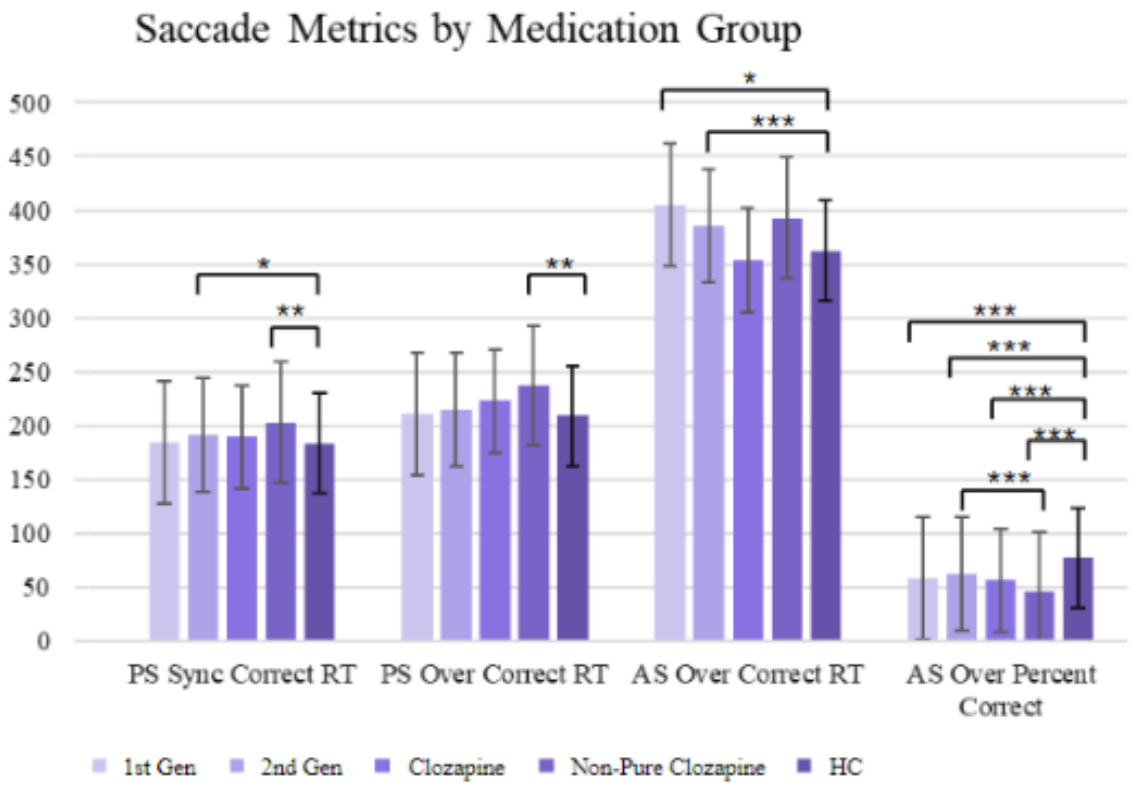
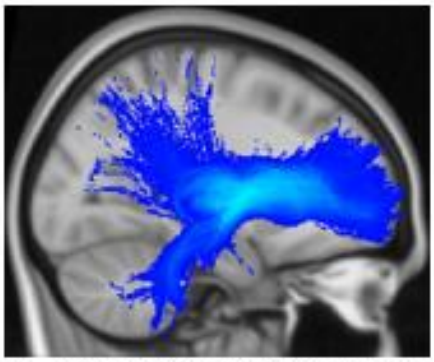
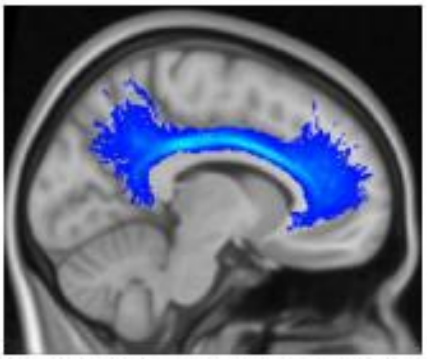


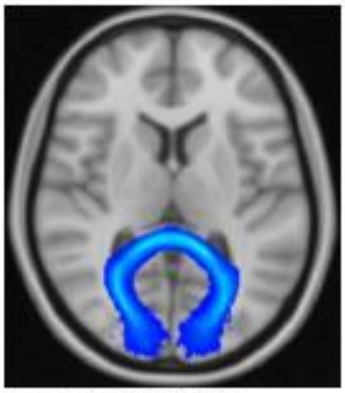
Figure 4. Bar Chart of Saccade Variables by Medication Group. Figure 4 contains the means of saccade variables by medication group. Error bars represent +/- 1 standard error and brackets indicate significant differences by group. *** represents a p-value ≤ .001, ** represents a p-value ≤ .01, and * represents a p-value ≤ .05. The prosaccade gap condition is not included in this chart as there were no significant differences by group.



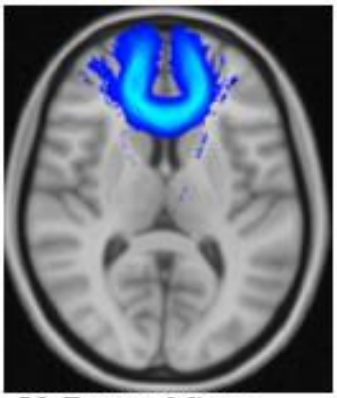
5a. Anterior Thalamic Radiation (L)



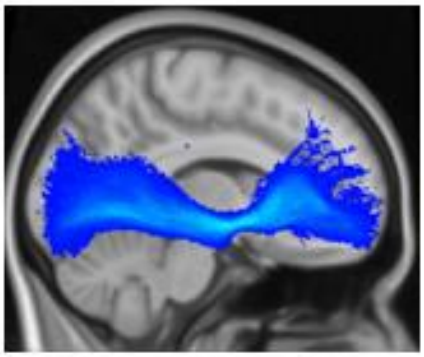
5b. Cingulum-Cingulate Gyrus Portion (L)



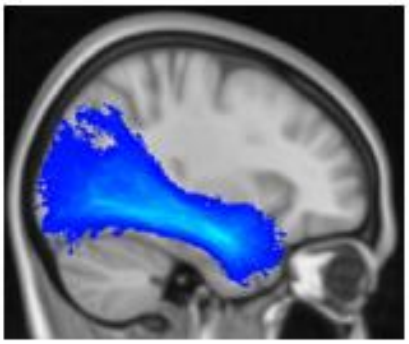
5c. Forceps Major



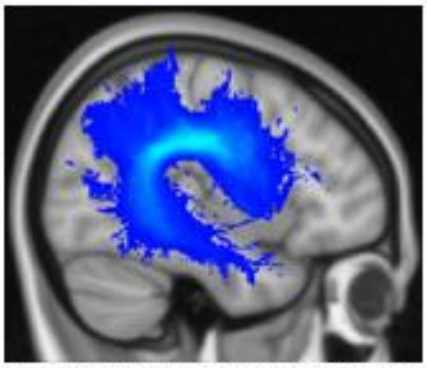
5d. Forceps Minor



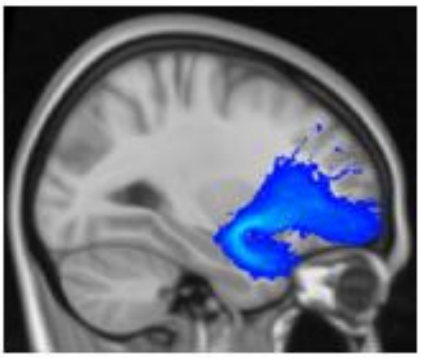
5e. Inferior Fronto-occipital Fasculus (L)



5f. Inferior Longitudinal Fascisulus (L)



5g. Superior Longitudinal Fasciculus (L)



5h. Uncinate Fasciculus

Figures 5a-h. Figures 5a-e are examples of some of the white matter tracts showing no significant difference in FA values when comparing those on clozapine to healthy individuals. Tracts used in the images are from the Johns Hopkins University White Matter Tractography Atlas and are shown using MNI 152 space. FSLeyes was used to visualize tracts and the gradient represents a 5% or greater likelihood of fibers belonging to the specified tract shown in dark blue to a 95% likelihood of fibers belonging to the tract shown in the lightest blue.

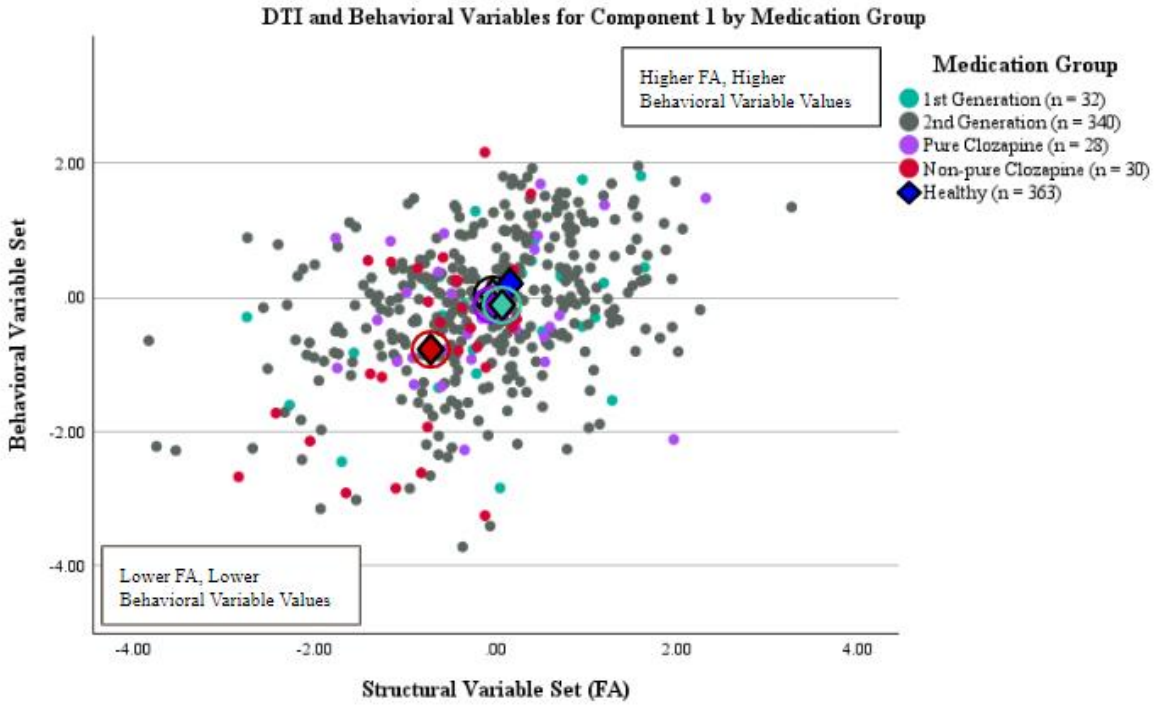


Figure 6. Scatterplot of component 1 variables by medication group. Structure variables are represented on the x-axis and primarily represent FA values for this component, and behavioral variables are represented on the y-axis. Behavioral variables are weighted positively for antisaccade overlap percent correct and the BACS composite scores, and negatively for pro and antisaccade overlap correct reaction times. Individual dots in the plot represent the value associated with each subject for each set of the component and are separated by medication group with each group being represented by a different color. Centroids (represented by diamonds) and standard error circles are included in colors corresponding to group colors. Healthy individuals were omitted from this plot for data visualization purposes, however the centroid for this group is represented in blue.

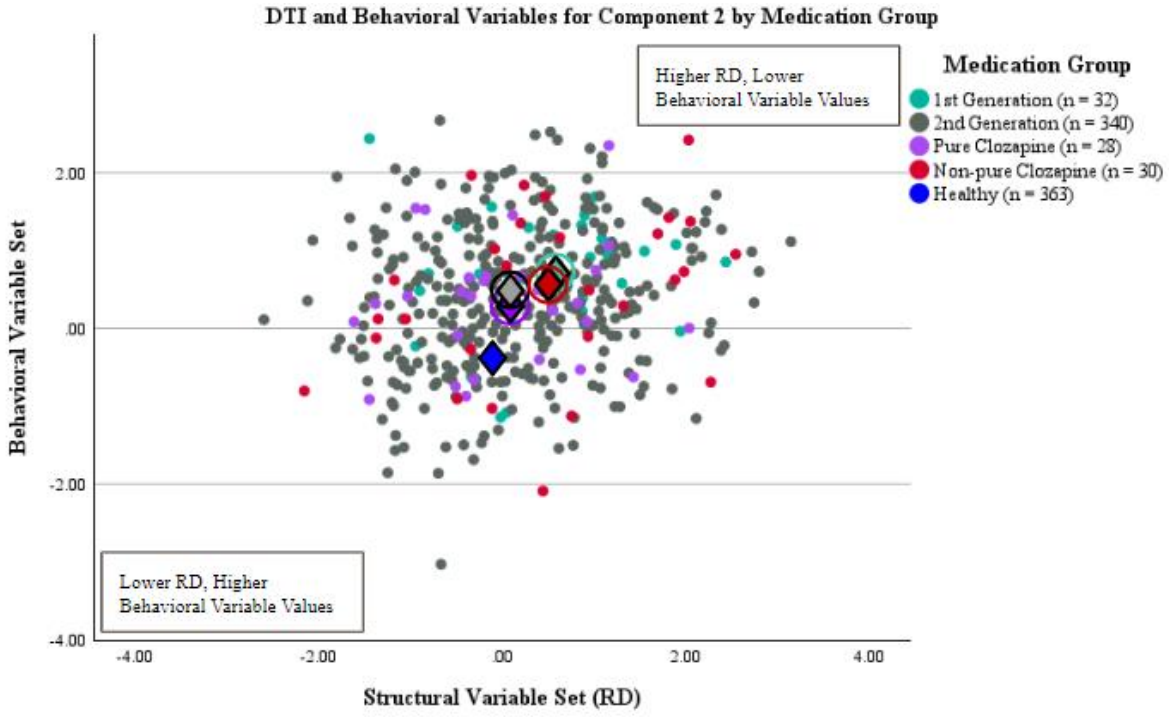


Figure 7. Scatterplot of component 2 variables by medication group. Structure variables are represented on the x-axis and primarily represent RD values for this component, and behavioral variables are represented on the y-axis. Behavioral variables are weighted negatively for all 4 variables. Individual dots in the plot represent the value associated with each subject for each set of the component and are separated by medication group with each group being represented by a different color with corresponding colors for centroids (marked by a diamond) and standard error circles. Healthy individuals were omitted from this plot for data visualization purposes, however the centroid for this group is represented in blue.

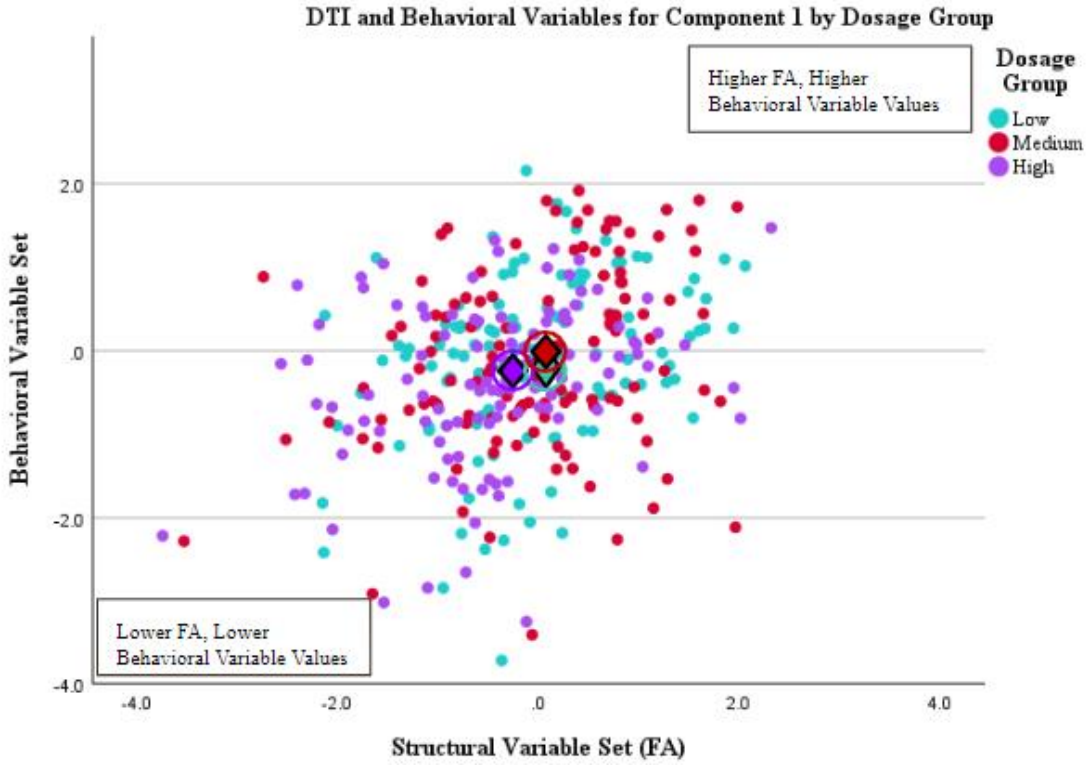


Figure 8. Scatterplot of component 1 variables by dosage group. Structure variables are represented on the x-axis and primarily represent FA values for this component, and behavioral variables are represented on the y-axis. Behavioral variables are weighted positively for antisaccade overlap percent correct and the BACS composite scores, and negatively for pro and antisaccade overlap correct reaction times. Individual dots in the plot represent the value associated with each subject for each set of the component and are separated by medication group with each group being represented by a different color. Centroids (represented by diamonds) and standard error circles are included in colors corresponding to group colors.

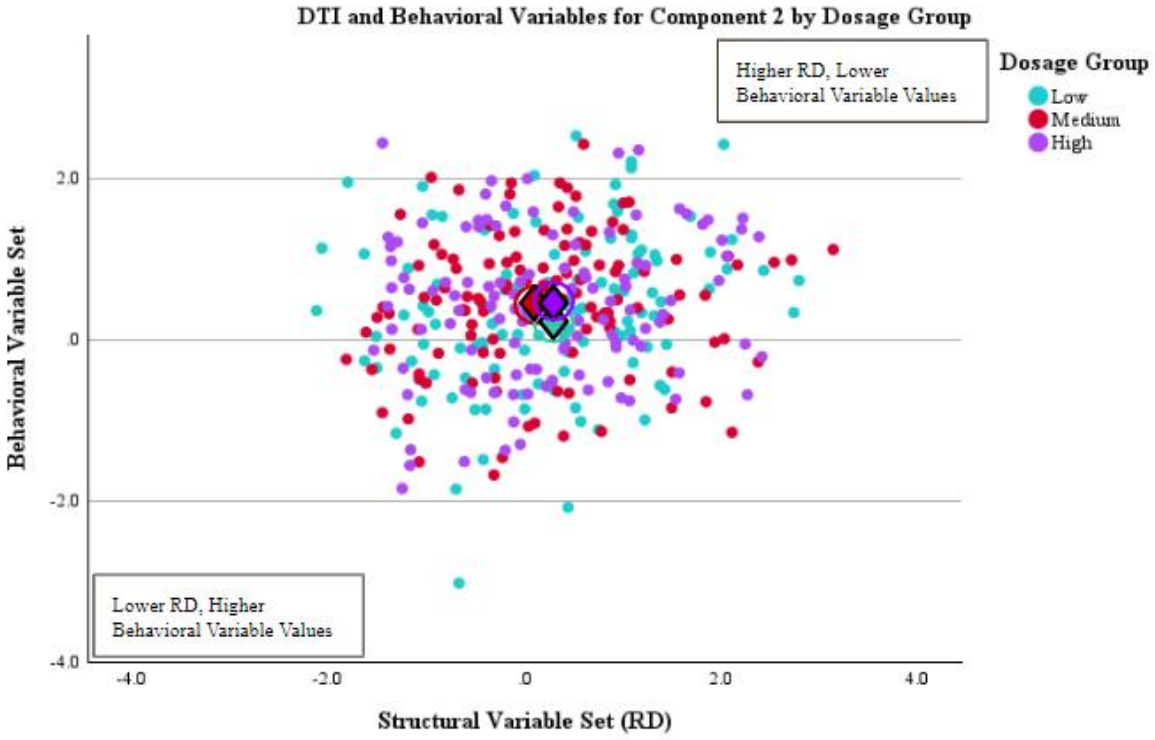


Figure 9. Scatterplot of component 1 variables by dosage group. Structure variables are represented on the x-axis and primarily represent FA values for this component, and behavioral variables are represented on the y-axis. Behavioral variables are weighted positively for antisaccade overlap percent correct and the BACS composite scores, and negatively for pro and antisaccade overlap correct reaction times. Individual dots in the plot represent the value associated with each subject for each set of the component and are separated by medication group with each group being represented by a different color. Centroids (represented by diamonds) and standard error circles are included in colors corresponding to group colors.