THE BASIC NEUROCOGNITIVE CONTINUUM (BANCC): MODELING THE AFFILIATION OF NEUROBIOLOGICAL AND COGNITIVE MEASURES IN PSYCHOSIS

by

HAILEY C. WARREN

(Under the Direction of Brett A. Clementz)

ABSTRACT

This project studied the relationships between cognitive performance and measures of brain structure and function in 2,793 persons with psychosis, their first-degree biological relatives, and healthy individuals recruited by the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP). Cognitive performance was estimated using the BAC and WRAT, and indices of neural structure and neurophysiology included structural MRI, neurobehavioral, and EEG measures. This association of cognitive performance (criterion) and neural measures (predictors) was examined using a mixed-effects regression model (iDEAS). The model yielded a common slope of the predictors on cognitive performance (slope=0.187, $p<.001$), indicating better overall brain structure-function was associated with better cognitive performance, as well as predictor-specific deviations from that common slope (called the BAsic NeuroCognitive Continuum, or BANCC). Differential identification of deviating variables, which were interesting by virtue of their possible importance for indicating neurobiology peculiar to psychosis, is possible through the BANCC and comparatively difficult through other methods.

INDEX WORDS: psychosis, cognitive performance, neurophysiology, MRI, EEG, mixed-effects regression, neurocognition, neurobiology

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DEDICATION

This thesis is dedicated to my cherished companion (my cat Romeo), my encouraging and understanding friends, and my wonderful family. I want to dedicate this to my parents, especially, for their tireless support, patient wisdom, and uncompromising love.

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INTRODUCTION

Cognitive performance, encompassing cognitive control and executive functioning, describes higher-order problem solving distinct from automatic or reflexive sensory processes (Diamond, 2013). These are the most commonly employed terms used to describe a holistic overview of the intactness, functionality, and efficiency of the neural systems(McTeague et al., 2016). Variations in performance on a number of cognitive functions occur across psychosis diagnoses (Hill et al., 2013; McCleery & Nuechterlein, 2019; McCutcheon et al., 2023) and among persons with diagnoses comorbid with schizophrenia (Zhu et al., 2019). This spectrum of cognitive performance is not unique to psychosis or psychiatric diagnosis, however, as it exists across all humans (Craddock & Owen, 2010; Uddin, 2021). Even in healthy populations, longitudinal studies have shown cognitive performance to be linked to physical health outcomes, prevalence of risk taking behaviors, and financial stability(Miller et al., 2011; Moffitt et al., 2011). Whether as a result of the environmental and social factors that contribute to psychiatric risk, or by nature of the pervasive and often degenerative effect of psychiatric disorders on the brain, deficits in cognitive performance have been shown to be associated with serious psychiatric disorders(Abramovitch et al., 2021). Accordingly, despite the communal nature of this aforementioned cognitive dimension, it is worth noting that persons with serious psychiatric conditions tend to present lower than the overall population average (Clementz et al., 2022; Fett et al., 2020).

Cognitive performance deficits have been associated with symptom severity and disease outcomes in psychopathology, as insufficient recruitment of cognitive circuits, or deficiency of

cognitive adaptability and internal command, has been linked to lower levels of symptom remediation and management (Green et al., 2000; Green et al., 2004; McTeague et al., 2016; Zhang et al., 2018; Zhu et al., 2019). These changes in clinical function are mirrored by, or perhaps a result of, decreases in the integrity of brain structure and function (Goodkind et al., 2015; McTeague et al., 2017). Such extensive associations lead researchers to theorize the existence of a transdiagnostic neuro-cognitive dimension accounting for broad psychiatric vulnerability (Caspi & Moffitt, 2018; Goldberg et al., 2015; McTeague et al., 2016). Previous dimensional attempts have supposed that there are not in fact specific classes of mental disorders, but that psychiatric risk is a severity scale encompassing all mental disorders, with each current diagnosis occupying a spot along the continuum (Caspi & Moffitt, 2018; Kotov et al., 2020; Kotov et al., 2017). These dimensional approaches were developed in response to the overwhelming heterogeneity observed within, and comorbidity existing across, existing DSM diagnoses(Cuthbert & Insel, 2013; Guloksuz & Os, 2018, 2021; Hengartner & Lehmann, 2017). Despite the attractive nature of consolidation of psychiatric categories to a single dimension, there is nonetheless the existence of a new problem, which is an evident lack of requisite diagnostic specificity, and impairment of the critical ability to tailor treatments to a single patient. One of the field's most prevalent challenges is the slow progress of precision psychiatry towards the ability to identify disease targets through laboratory tests at the individual level(Zhang et al., 2023).

Biomarker and Biotype based efforts have been a response to the lack of forthcoming biologically based clinical treatment targets in either traditional categorical or novel dimensional approaches, which have become the gold standard in other fields of medicine. These endeavors leverage a "bottom-up" approach, beginning with laboratory measures and organizing groups by

shared biological features, contrary to symptom-focused “top-down” approaches that have dominated the field(Keshavan et al., 2013). One such research effort of psychosis-relevant measures illustrates a continuum of severity across multiple variables (schizophrenia < schizoaffective < bipolar disorder < healthy) without evidence of neurobiological distinctiveness for any clinically defined psychosis diagnosis (Clementz et al., 2022)

A continuum of severity across measures and domains may imply a fundamental latent component, with a possible central attribute of cognitive performance. Craddock & Owen (Craddock & Owen, 2010) organized their domains of psychopathology around the ubiquity of a transdiagnostic cognition dimension. McTeague et al. (McTeague et al., 2016) also proposed a multi-trait neuro-cognitive continuum that captures brain structure and function. In clinical research guided by the existing taxonomy of the DSM, individual deviations on these neural measures are thought to be characteristic traits of fixed classes of diagnoses. Examples include prefrontal cortex dysfunction or gamma band asynchrony for schizophrenia, or elevations in inflammatory TNF (tumor necrosis factor) and IL (interleukin) proteins in major depression (Das et al., 2021; Lanquillon et al., 2000; Tsuchimoto et al., 2011; Wible et al., 2001). However, a neuro-cognitive model assuming a multi-trait approach supposes that differences on neural measures are not peculiar to any specific diagnosis. Instead, they are proximate representations of where an individual falls on the neuro-cognitive deficit-surplus continuum.

Evaluating the magnitude of such a construct as a neuro-cognitive continuum requires a large variety of measures across multiple domains and diagnostic groups (Abramovitch et al., 2021; McTeague et al., 2016). One of the purposes of multivariate and transdiagnostic research is to evaluate the validity of the existing “top-down” approach, to find if organizing principles outside of the traditional taxonomy better align with existing neurobiological patterns in the

population(Guloksuz & Os, 2021; Keshavan et al., 2013). In this project, we used the B-SNIP multivariate and transdiagnostic database to evaluate the possibility of an overarching neuro-cognitive dimension that captures many, or possibly a majority of, outcomes in psychosis research. The dimension of cognitive performance (the criterion) was estimated using the Brief Assessment of Cognition (BACS) and Wide Range Achievement Test (WRAT). Upon that quantitative dimension hundreds of neuroanatomical (FreeSurfer parcellations of 3T MRI brain structure), brain functioning (pro- and anti-saccade, the stop signal, EEG and ERP measurements), and clinical characteristics (the predictors) were regressed. A linear mixed model (Gibbons et al., 2019) derived subject-level relationships between cognitive performance and all predictors simultaneously, extending previous efforts to derive a multivariate neuro-cognitive dimension called the BAsic NeuroCognitive Continuum (or BANCC; (Tamminga et al., 2021)). Every variable was evaluated for its fit or divergence in relation to this dimension. These comparisons asked whether there are specific measures that depart from the BANCC, to evaluate if most people and measures of brain structure-function fall along one common neuro-cognitive continuum, and/or if there are unique neurobiological features that identify etiologically unique subgroups within idiopathic psychosis.

METHODS

Participants

Participant recruitment, interviews, and laboratory data collection were completed at B-SNIP sites (full details on recruitment and screening strategies are available in Tamminga et al., 2013(Tamminga et al., 2013). Recruitment occurred in Athens, GA (University of Georgia), Baltimore, MD (Maryland Psychiatric Research Center), Boston, MA (Beth Israel Deaconess Medical Center), Chicago, IL (University of Illinois-Chicago and University of Chicago), Dallas, TX (UT Southwestern Medical Center), Detroit, MI (Wayne State University), and Hartford, CT (Institute of Living). Cases were drawn, therefore, from academic and community mental health centers, small towns with large universities, large cities, inner cities, rural regions, affluent and less affluent areas. B-SNIP recruited a research sample, not an epidemiological sample; nonetheless, the large study numbers and broad geographical recruitment foster generalizability of the outcomes across the range of early- and mid-course to late-life idiopathic psychosis. The Institutional Review Board at those institutions approved the projects; participants provided informed consent prior to initiating study procedures.

Laboratory Procedures

After confirming study eligibility, subjects meeting inclusion criteria were scheduled for laboratory biomarker testing, taking place across a span of 2-3 days at recruitment sites. Recording and testing conditions and equipment, as well as stimulus presentation, were standardized across sites. Experimenters at each site were trained in identical laboratory procedures and monitored to ensure consistency across sites. No site effects were found to

influence group comparisons on any laboratory biomarker measure, as a result of these procedures.

Clinical Evaluations

B-SNIP clinical evaluations are described in Tamminga et al. 2013 (Tamminga et al., 2013). Clinically stable outpatients, relatives, and healthy persons were administered the Structured Clinical Interview for DSM-IV-TR diagnosis. In the current B-SNIP database, there are up to 1437 psychosis cases, 733 nonpsychotic first-degree biological relatives of those cases, and 623 healthy persons recruited from the community with data available for this project. Healthy persons were free of lifetime psychosis, recurrent mood diagnosis, and a history of psychosis or bipolar disorder in their first-degree relatives (see Table 1 for demographic information, and Tables 6 & 7 for medication information). Psychosis cases were limited to schizophrenia (n=579), schizoaffective disorder (n=434), and bipolar I disorder with psychosis (n=424). Table 8 provides demographic information stratified by those groups. Psychosis cases were also stratified into B-SNIP psychosis Biotypes (BT1, BT2, or BT3) using previously described methods (Parker et al., 2025); see Table 9 for demographic information stratified by Biotype. Participants were rated on the Birchwood Social Functioning (SFS; (Birchwood et al., 1990)), Montgomery-Asberg Depression Rating (MADRS; (Montgomery & Asberg, 1979)), Positive and Negative Syndrome (PANSS; (Kay et al., 1987)), and Young Mania Rating (YMRS; (Young et al., 1978)) scales (see Tables 10 & 11 for clinical information.

Cognitive Performance Quantification – The "Criterion"

Participants completed the Brief Assessment of Cognition in Schizophrenia (BACS), which covers multiple cognitive domains (Keefe et al., 2008; Keefe et al., 2006; Keefe et al., 2004). The BACS provides an excellent measure of psychosis-related cognitive performance

(Hill et al., 2013; Hochberger et al., 2016). Participants also completed the Wide Range Achievement Test-IV Reading subtest (WRAT;(Wilkinson & Robertson, 2006). The WRAT estimates school-related learning and perhaps premorbid potential (Keefe et al., 2005). Principal Component Analysis (PCA) of the BACS and WRAT scores yielded one significant component; the loadings are available in Table 2. A cognitive performance score using the PCA solution provides the "criterion" (x-axis) variable in subsequent analyses (see Table 1 for descriptive statistics).

Multiple Variable Biomarker Panel – The "Predictors"

Papers on individual laboratory measurements provide extensive data collection and analysis details (Clementz et al., 2016; Parker et al., 2025). The variables occupy four domains: (i) brain structure quantified from MRI; (ii) behavioral performance of brain functioning quantified by saccade and stop signal performance; (iii) neurophysiological brain functioning quantified by event-related (ERP) and electroencephalography (EEG) measurements of neural function; and (iv) clinical features to capture current clinical state and social functioning. The behavioral and ERP/EEG measures are used for Biotypes creation (Parker et al., 2025). The B-SNIP team previously illustrated that medications do not account for group differences on those biomarker features (Parker et al., 2025). Participants across all psychosis Biotypes are also largely on the same medications, although their biomarker profiles differ (Table 6 & 7). The following is a brief description of predictors and their quantifications.

Structural MRI Data Collection and Variables

Methods for the MRI platform and data collection are as have been described previously (Ivleva et al., 2013; Ivleva et al., 2017). Magnetic Resonance Imaging (MRI) whole-brain structural data were collected using 3 Tesla scanners. Full MRI scanning parameters and scanner

specifications are available in Table 3. Whole brain high resolution (voxel = 1 x 1 x 1.2 mm) T1-weighted MPRAGE or IR-SPGR sequences were acquired following the ADNI protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/).

The B-SNIP team processed images blind to the participants' group membership and other clinical characteristics. Variables quantifying cortical structures – thickness, area, volume (region- and lobe-based), and gyrification of gray matter– were derived via FreeSurfer v .7.1.0 (see (Guimond, 2022; Padmanabhan et al., 2015). Gyrification was estimated using the local Gyrification index, which is an additional FreeSurfer module (Schaer et al., 2008). Estimation of the four previously mentioned neuroanatomical measurements was completed using two FreeSurfer atlases- the Desikan-Killany atlas (Desikan et al., 2006), and a lobe-wise Cortical Parcellation atlas that summed all DKT labels into their respective lobes, excluding the insula (see https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation for categorization). Subcortical structures were estimated using the Automatic Subcortical Segmentation, or "Aseg" atlas.

These data were harmonized to account for scanner differences using ComBat in Python- a technique for removing non-biological variance due to Magnetic Resonance Imaging (MRI) scanner differences in multi-site datasets (Fortin et al., 2017). ComBat utilizes an Empirical Bayes (EB) framework to estimate information across variables and sites/scanners in order to better estimate data points and balance the dataset (Berardi 2024, under review). Harmonization was first carried out in the healthy persons reference group, and then the resulting data framework was applied to the whole sample, to preserve group-related differences (psychosis, relatives, etc.). Harmonized structural MRI data was then standardized within each measure in order to preserve deficit and surplus continuums within each measure while setting all measures

on the same scale. A total of 414 FreeSurfer-based measures were obtained: 409 measures of brain structure (306 cortical and 103 subcortical), 4 ventricular volumes and 1 of white matter hypointensities. A listing of all MRI variables is in Table 12.

Behavioral Data Collection and Variables

Behavioral measurements come from (i) pro- and anti-saccades (McDowell & Clementz, 2001; McDowell et al., 2012) to assess speed of visual orienting, goal maintenance, and inhibitory control under perceptual conflict, and (ii) a stop signal task (Lipszyc & Schachar, 2010) to assess adequacy of inhibitory control using speeded motor responses. Pro- and anti-saccade tasks were performed under identical conditions using Eyelink II head-mounted infrared headsets (500 hz sampling rate) and the corresponding SR Research Ltd. Control platform. Stimuli were programmed using Presentation software (Neurobehavioral Systems, Inc., Berkeley, CA,) and presented on 22-inch CRT monitors in completely darkened rooms. Task order always began with prosaccade tasks, followed by antisaccade-overlap. Trials were arranged pseudo-randomly within each task and condition so that trials were evenly split between +/-10- and 15-deg displacements. To help facilitate participants' understanding of the antisaccade task, an abbreviated practice block was performed prior to the start of the task.

Prosaccades (looking at a visual cue) assess speed of visual orienting. Participants simply look quickly and accurately at a newly appearing visual stimulus. Alternatively, antisaccades (Hallett & Adams, 1980) assess at least two abilities: (i) inhibitory control, because the visual stimulus and required response location are incompatible, and (ii) goal maintenance, because subjects must remember the response requirement over time (Ethridge et al., 2009; McDowell & Clementz, 2001). Participants look as quickly and accurately as possible to the mirror image location of a peripheral cue. Data were scored by trained research assistants, and response

latencies and percentage of correct responses were quantified using MatLab (MathWorks Inc., Natick, MA, USA)(Huang et al., 2022). PCA reduced the pro- and anti-saccade variables to two "bio-factors", one for speed of visual orienting and one for antisaccade performance. Two thousand four hundred and ninety participants had usable saccade data.

The SST measures efficiency and adequacy of cognitive control when response preparation and the subsequent movement requirement are conflicted(Ethridge et al., 2014). Subjects see a 'Go' cue to the left or right of central fixation. On a minority of trials, a 'Stop' signal is presented. Participants are instructed to respond to the Go cue as quickly as possible unless they encounter the Stop signal. A baseline task consisting of 50 consecutive Go trials, evenly and randomly distributed to cues on the left and right side of the screen, was administered to assess baseline reaction time to Go cues. Strategic slowing (difference between response latencies on baseline Go trials and Go trials during Stop Signal performance) and proportion of Stop Signal errors were used in Biotype construction (Clementz et al., 2016). PCA (Covariance Matrix; Promax Rotation; Kappa 4) reduced those variables to one SST bio-factor. Two thousand one hundred and eighty-one participants had usable SST data.

Neurophysiological Data Collection and Variables

Data collection via dense array electroencephalography occurred during (i) auditory paired stimuli (Freedman et al., 1987) and (ii) auditory oddball paradigms (Squires et al., 1975). These paradigms assess the neural dynamics of preparation for and recovery from auditory sensory activations, neural responses to stimulus salience, neural differentiation of relevant from irrelevant auditory stimuli, context updating in available memory, and allow for quantification of ongoing and intrinsic neural activity.

For the paired stimuli paradigm, analyses generally followed procedures established in Hamm et al.(Hamm et al., 2014) and Clementz et al.(Clementz et al., 2016). For this task, participants passively listened to up to 150 auditory stimuli pairs with a short (500 msec) interval between the two stimuli and a long (8 to 10 sec) interval between the pairs.

For the oddball task, analyses generally followed procedures established in Ethridge et al.(Ethridge et al., 2014) and Clementz et al.(Clementz et al., 2016). For this task, participants listened to hundreds of auditory stimuli occurring every 1 to 1.5 sec. Most stimuli were the same (1000-Hz tones) and are called 'standards.' Some of the stimuli, randomly interspersed with the standards, were different (1500-Hz tones), and are called 'targets.' Targets elicit a different brain response from the standards, with the most prominent the so-called p300 (a positive voltage waveform in the ERP most prominent over central parietal lobe sensors occurring 300 to 400 msec after stimulus onset).

Data pre-processing methods are as detailed in Hamm et al. 2014 (Hamm et al., 2014). Raw EEG data were inspected for bad sensors, which were interpolated (<5% per subject) using spherical spline interpolation (BESA 5.3; MEGIS Software, Grafelfing, Germany). Data were converted to an average reference and digitally band-pass filtered. Blink and cardiac artifacts were inspected for and identified utilizing independent components analysis (ICA), and subsequently removed (EEGLAB 9.0).

ERP and EEG data are quantified in multiple ways to maximize use of available information using all sensors and time points, with brain responses extracted from the temporal and frequency domains. Scoring data in the temporal domain yields information on the strength of brain signals in voltage units at specific time points (50, 100, 200, or 300 ms after stimulus onset), and called event-related brain potentials (ERPs). Scoring in the frequency domain yields

information on brain signals in particular frequency ranges (e.g., delta, theta, alpha, beta, gamma); this information is also quantified as a function of time (e.g., gamma activity in the first 100 msec after stimulus onset). Extracting voltage and frequency provides more information on complex brain responses than is possible using either approach alone. Dimension reduction for these bio-factors were conducted separately for paired-stimulus and oddball paradigms, utilizing first a frequency-wise PCA (Covariance matrix, Promax Rotation, Kappa 3 with Kaiser normalization) of evoked power, and then a spatial PCA (Covariance matrix, Promax Rotation, Kappa 3 with Kaiser normalization)(Parker et al., 2020; Parker et al., 2021). Statistical integration over ERP/EEG from the paired stimuli and oddball administrations (Parker et al., 2025) yields four ERP magnitude bio-factors (paired ERPs, oddball ERPs, frontal p300, and paired S2 response) and three intrinsic activity bio-factors (non-task intrinsic activity or IEA, ongoing activity during paired stimuli, and ongoing activity during oddball). Two thousand three hundred and ninety-seven participants had usable EEG/ERP data.

Clinical Data and Variables

The clinical assessments outlined above (SFS, MADRS, PANSS, YMRS) provided information for constructing clinical variates. Following the method of (Clementz et al., 2020), the B-SNIP team used canonical discriminant analyses to create quantitative symptom dimensions for DSM diagnoses and B-SNIP Biotypes. Rather than use all 57 item-level ratings across the four clinical scales, they restricted the discriminant analyses to the top ten items for DSM diagnoses and Biotypes from the Clementz et al. 2023 decision tree algorithm called ADEPT (Clementz et al., 2023).

Two discriminant analyses were conducted, one for DSM schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis as the criteria, and another for B-SNIP psychosis

Biotypes with BT1, BT2, and BT3 as the criteria. For DSM there were two significant functions: DSM_CLIN1 describes general psychosis features (delusions, avolition, disorientation) while DSM_CLIN2 describes emotional/affective dysregulation (see Table 10). For psychosis Biotypes there was one significant function: BT_CLIN1 describes thought disorder and avolition (see Table 11). These three variates were used as clinical predictors.

Model Design

A problem in computational neuroscience is the regression of multiple predictors on a single outcome. Many models identify key predictors from a high dimensional variable set (e.g. Lasso regression; (Tibshirani, 1996). As the number of predictors increases, however, efficiency decreases. (Gibbons et al., 2019) introduced an approach based on mixed-effects regression models that provide simultaneous estimates of all predictors on a single outcome. Because the predictors are treated as clusters in the mixed-model, efficiency increases with increasing number of predictors because they borrow strength from each other. The overall association between cognitive performance and the 428 brain structure-function and clinical variable-specific associations were examined using the High Dimensional Empirical Bayes Screening (iDEAS) algorithm (Gibbons et al., 2019). This model uses a high-dimensional set of predictors, treated as clusters, and predictor-specific associations are simultaneously estimated using empirical Bayes estimates. Data were first standardized within each variable to preserve deficit to surplus continua while putting all measures on the same scale. SuperMix (Scientific Software International) was then used for model fitting.

Goodness of fit of individual predictors to the overall function was assessed using visual inspection of the caterpillar plot and Bonferroni-adjusted confidence intervals derived from empirical Bayes estimates of predictor-specific associations with cognitive performance.

Variables with confidence intervals not including the overall canonical slope were identified as possible deviating variables. In relation to cognitive performance, variables more significantly associated with the overall function have steeper slopes and those less associated with the overall function have shallower slopes. Any variables deviating from the overall function were integrated via PCA. One PCA integrated variables with more significant slopes on cognitive performance (more highly associated), and another PCA integrated variables with shallower slopes (less associated). The more and less associated variables were analyzed by group membership using canonical discriminant analyses. All statistics were based on $p < .01$.

RESULTS

The Overall Function Fit (BANCC)

The linear mixed effects model converged in four iterations. Across all 428 variables and 769,335 total observations (variables by participants) there was an overall slope of .187 (SE = .0034, z = 54.91, p <.001) and intercept of .051 (SE = .0011, z = 45.81, p <.001). Figure 1 plots each subject's average predictor score against their cognitive performance. This analysis and plot illustrate there is a significant relationship between the overall brain structure-function variable set and cognitive performance, called the BANCC.

Figure 1 also shows the plots stratified by psychosis probands, the first-degree biological relatives of those probands, and healthy persons. The slopes of the linear functions were statistically significant for all three groups (t's > 4.51, p's < .001). Comparison of slopes, however, shows the probands with a significantly steeper slope of the predictors on cognitive performance (.204, SE = .013) than both the relatives (.098, SE = .022) and healthy groups (.113, SE = .022), who do not significantly differ.

Individual Predictor Fits to BANCC

Fit to the overall function slope- here, the "BANCC"- was assessed through complimentary Bonferroni-adjusted 99% confidence intervals derived from empirical Bayes Estimates and visual inspection of the caterpillar plot. Figure 2 shows this caterpillar plot, with each predictor and its associated confidence interval ordered from most negatively deviating to most positively deviating. Negative deviation values indicate that the predictor is less strongly related to cognitive performance, and positive values indicate that the predictor is more strongly

related to cognitive performance. At deviations of +/- .10 there is a visible change in the strengths of relationships between the predictors and cognitive performance (see red dots). Between these points, the plot illustrates a linear trend of deviation from the overall BANCC slope. However, for variables with deviation values greater than .10 and less than -.10, there is a visible acceleration of mean deviation values, represented by the blue dots between the confidence intervals. Because of this change in the relationship, I used these points to guide the stringency of the confidence intervals for cutoff in order to have accurate alignment with the canonical function.

Individual Predictors Deviating from the BANCC

Out of the 428 predictors, 388 (90.7%) had deviations of less than ±.10 from the canonical slope (see Figure 2, Table 4, and Table 5). Structural MRI measures of cortex and subcortex (across volume, thickness, area and gyrification) had the highest percentage of variables fitting the overall function (from 91-97%). The behavioral and physiological measures (called "bio-factors"; 55%) and MRI signal deviations and clinical measures (called "other"; 58%) had lower percentages of variable fitting the overall function. This difference in pattern of deviations across variable classes was statistically significant, X^2 (6) = 33.9, p <.001. Figure 2 also shows the distributions averaged over variables with stronger (standardized slope = .320) and weaker (standardized slope = .017) associations with cognitive performance.

Data Reduction of BANCC and Deviating Variables

First average score of the 388 variables was computed, which defined the overall function on cognitive performance (called the **BANCC**). Second, to probe the relationships between the 13 variables more strongly associated with cognitive performance than the BANCC, a Principal Component Analysis (PCA: covariance matrix; promax rotation) was conducted. The scree plot

indicated one component (see Table 13 for component loadings). The multiple and distributed brain volume measures loaded highly on this component, so it is called “Global Brain Volume”. Third, to probe the relationships between the 27 variables less strongly associated with cognitive performance than the BANCC, a second PCA was conducted. The scree indicated eight components (see Table 14 for component loadings). Component 1 captures ventricular volumes (“Ventricular Volume”). Component 2 captures lateral and latero-dorsal subnuclei of the thalamus (“Lateral Thalamic Volume”). Component 3 captures intrinsic EEG activity (“Intrinsic EEG”). Component 4 captures hypothalamic volumes (“Hypothalamus”). Component 5 captures cingulate thickness (“Cingulate Thickness”). Component 6 captures pericalcarine cortex thickness (“Pericalcarine Thickness”). Component 7 captures entorhinal cortex thickness (“Entorhinal Cortex Thickness”). Component 8 captures medial thalamic nuclei volume (“Medial Thalamic Volume”).

Group Comparisons using BANCC and Deviating Components

The above 10 variables were used in two canonical discriminant analyses: (i) DSM probands and healthy groups, and (ii) Biotype probands and healthy groups. Group differences on discriminant functions were evaluated using Tukey B. These analyses addressed whether there is only a dimensional pattern of group differences. If not, then additional patterns may capture unique signatures related to psychosis neuropathology.

In the DSM analysis, there was only one significant discriminant function, X^2 (30) = 145.9, $p < .001$, with a canonical correlation of .31. This function was largely associated with the BANCC (.57) and Global Brain Volume (.49), so lower scores are associated with worse cognitive performance and associated neural correlates of cognitive performance combined with lower cortical volumes. Statistical comparisons between groups illustrate that the schizophrenia,

schizoaffective, and bipolar psychosis groups, who did not differ, had significantly lower scores than the healthy group (see Figure 3).

In the B-SNIP Biotype analysis, there were three significant discriminant functions: Function 1 X^2 (30) = 799.3, $p < .001$, with a canonical correlation of .66; Function 2 X^2 (18) = 143.4, $p < .001$, with a canonical correlation of .31; Function 3 X^2 (8) = 29.9, $p < .001$, with a canonical correlation of .16. The first function is overwhelmingly associated with Intrinsic EEG (.99), so persons with higher scores have higher intrinsic neural activity. Biotype-2 cases had the highest and Biotype-1 cases the lowest scores (Biotype-2 > Biotype-3 > Healthy > Biotype-1; see Figure 3). The second function was primarily associated with the BANCC (.70) and Global Brain Volume (.66), so is like the significant DSM function. Biotype-1 and Biotype-2 groups had significantly lower scores than Healthy and Biotype-3 groups ([H = BT3] > [BT2 = BT1]; see Figure 3). The third function was primarily associated with Global Brain Volume (.48), and Lateral Thalamic Volumes (-.46), so persons with lower scores have modestly smaller cortical gray matter volume and larger volumes of lateral thalamic nuclei. Biotype-3 had lower scores than the other groups, who did not differ ([H = BT2 = BT1] > BT3; see Figure 3).

The 10 deviating components were also tested for first-degree relative differences. First, relatives were compared based on classification of the DSM proband to who they were related. For DSM-grouped relatives, there were no differences between groups for any of the 10 deviating components, $F's < 2.09$, $p's > .10$. For psychosis Biotype-grouped relatives, there also were no differences between groups for any of the 10 deviating components, $F's < 2.19$, $p's > .089$. Consequently, there were also no differences between relative groupings on the discriminant function variates.

DISCUSSION

This project evaluated the relationship between cognitive performance and multiple brain structure-function measures in a transdiagnostic psychosis sample. It assessed whether most participants and their measures of brain structure-function are captured by a common neuro-cognitive continuum. This possibility is an organizing principle of dimensional theories for serious psychopathology (Abramovitch et al., 2021; Caspi & Moffitt, 2018). Against this neuro-cognitive continuum, called the BANCC, it also evaluated whether certain measures, not captured by this dimension, are neurobiological signatures for etiologically distinct subgroups within idiopathic psychosis.

Sequential analyses yielded outcomes significant both to our understanding of neurocognition as well as our ability to isolate idiopathic psychosis. First, there is a significant relationship ($r = .32$) between cognitive performance and all 428 neurophysiological and structural predictors, and that 91% of these predictors fit the function (the BANCC). The strength of this relationship differed across groups: it was stronger for probands ($r = .38$), and more moderate for first degree relatives ($r = .21$) and healthy persons ($r = .17$). Of the variables that deviated from this overall function, there were two classes- those more highly associated with cognitive performance ($r = .38$) than the BANCC, and those that were less highly, or not at all, associated with cognitive performance ($r = .04$) than the BANCC. These variables are interesting due to their utility in discriminating independently derived psychosis biotypes (Clementz et al., 2022). These deviating variables did not, however, provide readily discernable information about predisposition for psychosis, as determined by analysis of probands' first-degree relatives. It is

important to note that while the interpretation of these conclusions may not be affected, it is nonetheless necessary to consider that metrics of cognitive performance may not be fully representative of an individual's fullest cognitive capacity, and the group sizes of subjects across psychosis, relatives, and healthy persons in this study are not reflective of the natural population distribution.

Neuro-Cognitive Continuum

About 91% of included variables are captured by the transdiagnostic canonical function, called the Basic NeuroCognitive Continuum (BANCC). as proposed by McTeague et al. and others (Clementz et al., 2024; McTeague et al., 2016; Tamminga et al., 2021). Within this function, on average, persons with psychosis fell towards the deficit end on the cognitive performance and neurobiological variables (cognitive performance z-score score of -0.31) in relation to their relatives (0.27) and healthy persons (0.41). This deficit end captures scores indicating lower brain volume and area, lower cortical thickness, smaller subcortical structures, reduced gyrification, reduced ERP amplitudes, poorer saccadic performance, and more clinically severe symptom profiles. A vast majority of the structural MRI variables fit this function (91-97%), which reflects whole brain involvement in the tasks used to measure cognitive performance in psychosis research, which index executive function, memory, reasoning, decision making, and problem solving. Gray matter reduction has been identified as a biomarker for cognitive deficits in numerous other psychiatric and neurological conditions characterized by neurodegeneration and neurological abnormalities including, but not limited to- Alzheimer's and Parkinson's, as well as psychiatric disorders such as depression, OCD, and addiction (Erp et al., 2018; Goodkind et al., 2015; Hettwer et al., 2022; Ivleva et al., 2013; Ivleva et al., 2017; van de Mortel et al., 2022). The shared relationship described by the BANCC illustrates the strong

gravitational attraction of cognitive performance for brain structure-function variables used in neuropsychiatry, though the pervasiveness of this cognitive dimension does not disprove the simultaneous existence of distinct disease categories (Clementz et al., 2024).

Deviators from the BANCC

About 9% of the brain structure-function variables deviate from the BANCC. Some of these measures are more significantly associated with (positively deviating from) and others are unrelated to (negatively deviating from) cognitive performance. Analysis of positively deviating variables highlighted the strong association of nonspecific cortical volumes and antisaccade performance with cognitive performance, which are consequently the first to take "hits" in neurodegeneration due to neurological or psychiatric disorders, like Alzheimer's and Parkinson's diseases (Craddock & Owen, 2010; Huang, 2022; Mosimann et al., 2005; Reilly et al., 2014). On the other hand, analysis of negatively deviating variables emphasized variables associated uniquely with psychosis or previously identified as biofactors for differentiating psychosis subgroups(Clementz et al., 2016; Parker et al., 2025). The marked cognitive performance deficits accompanying psychosis generate a unique problem, in that it is difficult to determine whether changes observed in this population are due to the unique biological signatures of this psychiatric phenomenon or are the result of these hallmark cognitive performance discrepancies. These analyses have sought to demonstrate that by modeling the BANCC it is possible to collect those variables driven by cognitive performance, leaving behind distinctions unique to the pathology of idiopathic psychosis.

Probes of the associations of these deviating variables reveal several findings with taxonomical implications, which will hopefully provide useful information to further classification efforts. First are the results of the two discriminate analyses conducted on the

deviating variables and BANCC, first by DSM diagnosis and second by B-SNIP biotype. The first showed no separation of schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis on their cognitive performance-global brain structure-function relationships (see Figure 3). The second demonstrated that on this same function, Biotypes 1 and 2 had a shared deficiency from both BT3 (which demonstrated an intermediate level of deficiency) and healthy persons. This illustrates a lack of meaningful segmentation within "gold-standard" diagnostic subgroups, even on the sole variables showing marginal difference, in marked contrast to novel biomarker-based systems.

In this second analysis it was also revealed that the variables with the highest utility for discriminating Biotypes were those that are recognized as psychosis bio-signatures. These bio-signatures are disease-related pathologies isolated from differences accounted for by comparative deficits in cognitive performance. The results of the present paper indicate two such variables. First is intrinsic neural activity, or IEA, which is a function of background neural activity against which a signal-specific neural response is generated and the strength of that signal-specific response: it is also often conceptualized as signal-to-noise ratio, or SNR. On the discriminate factor encompassing such variables, biotype groups express the pattern established in previous B-SNIP analyses (BT1 < HC < BT3 < BT2: See Figure 3)(Hudgens-Haney et al., 2017; Hudgens-Haney et al., 2018), providing additional independent validation of these previous findings.

New information supplementing these preexisting findings includes the final discriminate factor for Biotype-driven analysis- the third component comprised mainly of lateral thalamic volume measures. In this component it was found that BT3 significantly differed from either healthy persons or other proband groups, which possibly hints at one factor for the origin of

thought distortions in this Biotype. Disruptions in the thalamus can lead to symptoms resembling psychiatric conditions, including idiopathic psychosis (Carrera & Bogousslavsky, 2006). The lateral portions of the thalamus serve a number of purposes, but novel research supports the theory that these structures serve as an "inhibitory switchboard" for other regions of the brain(Fratzl & Hofer, 2022). As a consequence, dysregulation in these thalamic substructures has impacts on sensory processing, leading to impaired emotion regulation (Frank et al., 2014) and context-inappropriate inhibition of many cortical regions and their associated behavioral functions, including appetite, threat defense, and motivational state (Fratzl & Hofer, 2022). Furthermore, communication of ocular information to the cortex is driven by the lateral geniculate nucleus of the thalamus, and abnormalities in such communication are associated with worse hallucinations and greater negative symptoms(Bannai et al., 2020). Pathophysiological associations of the thalamus, combined with demonstrated reductions in cortical volumes, may offer insight into the etiology of psychosis for BT3. The possible future transference of such conditions as psychosis from idiopathic to explicable, and often correspondingly from psychiatry to neurology, may feel to some in the field like losing ground. It is important to consider in these circumstances that a better understanding of the biological precipitants of these syndromes is not a discreditation of the study of psychiatry, but a validation of the experiences of those with these conditions, and thereby the necessity of this discipline.

Taxonomical Future

Apart from findings specific to the validation and supplementation of B-SNIP biotype arrays, this analysis has additionally yielded support towards biological based classification systems for serious psychiatric illness. Assessment of the BANCC function and these two groups of deviating variables revealed that the traditional DSM taxonomy was primarily influenced by

the cognition driven BANCC function, for a homogenous result, while discrimination by Biotype was primarily influenced by the neurobiologically and neurophysiologically discrete deviators, for a clear separation of subgroups. Heterogeneity in psychiatry has long since been a pressing issue for the ability to diagnose and treat disorders efficaciously (Zhang et al., 2023), and this has generated a multitude of theories regarding the correct taxonomical approach (Caspi & Moffitt, 2018; Kotov et al., 2017). This project posits that categorical approaches (biotypes) and continuous measures (the neurocognitive continuum) are not antithetical to each other, but instead are mutually beneficial (Clementz et al., 2024; Fulford & Handa, 2018). A dialectical model including the coexistence of biologically discrete subcategories of disease with indices of deficit and surplus variations in the natural population allows for the identification of unique disease-related pathology as well as the assessment of clinical and cognitive extremes for risk prediction.

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Table 1: Demographic Characteristics of Psychosis, Relative, and Healthy Groups

Characteristic	Psychosis n = 1437	Relatives n = 733	Healthy n = 623
Mean Age (SD)	37.68 (12.19)	41.21 (15.67)	36.17 (12.40)
Sex (%)			
Male	50.2%	31.9%	42.1%
Female	49.8%	68.1%	57.9%
Ethnicity (%)			
Not Hispanic	88.7%	91.5%	87.6%
Hispanic	11.1%	8.5%	12.2%
Unknown	0.2%	0%	0.2%
Race (%)			
Black	39.3%	30.2%	27.3%
American Indian	0.5%	0.4%	0.2%
Asian	2.9%	1.5%	7.9%
White	49.4%	64.7%	58.7%
Multiracial	5.0%	1.2%	3.0%
Hawaiian/Pacific Islander	0%	0%	0.3%
Other	2.9%	2.0%	2.6%
Mean Global Functioning (SD)	52.81(12.82)	74.89(13.46)	84.97(6.68)
Mean Proband SES (SD)	47.83(14.58)	39.37(17.36)	35.67(13.67)
Mean Family SES (SD)	42.16(16.26)	42.07(15.82)	37.7(14.5)
Mean Cognitive Performance Z-Score (SD)	-0.31 (0.98)	0.27(0.97)	0.41(0.84)

Table 2: Cognitive Performance Pattern Matrix

Cognitive Performance Pattern Matrix	
Total BACS	**0.81**
WRAT - Reading	**0.81**

Table 3: MRI Image Parameters

*In-plane resolution matrix (Z * Y)*	*Flip Angle*	*Inversion Time (ms)*	*Echo Time (ms)*	*Repetition Time (ms)*	*Slice Thickness (mm)*	*Field Strength (T)*	*Scanner location*	*Manufacturer /model*		
256 x 256	*8*	*1100*	*2.996*	*6.744*	*1.2*	*3*	*Beth Israel Deaconess Medical Center, Boston MA*	*Signa Excite*	*Boston 1*	*T1 MPRAGE image parameters*
256 x 256	*8*	*650*	*2.848*	*6.988*	*1.2*	*3*		*Signa HDxt*	*Boston 2*	
256 x 256	*11*	*400*	*2.848*	*6.988*	*1.2*	*3*		*Signa HDxt*	*Boston 3*	
256 x 256	*11*	*400*	*3.052*	*7.38*	*1.2*	*3*		*Signa Discovery MR750*	*Boston 4*	
256 x 256	*11*	*400*	*2.832*	*6.968*	*1.2*	*3*	*University of Georgia, Athens, GA*	*Signa HDxt*	*Georgia*	
256 x 256	*8*	*1100*	*2.996*	*6.988*	*1.2*	*3*	*University of Illinois*	*Signa HDx*	*Chicago 1*	
256 x 256	*9*	*850*	*3.10*	*6.788*	*1.2*	*3*	*University of Chicago,*	*Philips Achieva*	*Chicago 2*	
256 x 256	*8*	*850*	*3.13*	*6.809*	*1.2*	*3*	*UT Southwestern Medical Center, Dallas, TX*	*Philips Achieva*	*Dallas 1*	
256 x 256	*9*	*850*	*3.10*	*6.8*	*1.2*	*3*			*Dallas 2*	
256 x 240	*9*	*900*	*2.89*	*2300*	*1.2*	*3*	*Harper University Hospital,*	*Siemens TrioTim*	*Detroit*	
256 x 240	*9*	*900*	*2.91*	*2300*	*1.2*	*3*	*John Hopkins*	*Siemens TrioTim*	*Baltimore*	
256 x 240	*9*	*900*	*2.95*	*2300*	*1.2*	*3*	*Olin Neuropsychiatry Research Center, Hartford CT*	*Siemens*	*Hartford 1*	
256 x 240	*9*	*900*	*2.95*	*2300*	*1.2*	*3*		*Siemens Skyra*	*Hartford 2*	
256 x 240	*9*	*900*	*2.95*	*2300*	*1.2*	*3*			*Hartford 3*	

Parallel?	*No*	*No*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*No*	*No*	*No*	*Yes*
	Note: T, Tesla; mm, millimeter; ms, millisecond													

Table 4: Variables by Category Fitting the Canonical Function

Variable Class	# Fit	# Deviate	# High / # Low	% Fit
Biofactors	5	6	1 / 5	45%
Subcortical	105	11	0 / 11	91%
Frontal	100	5	3 / 2	95%
Temporal	82	6	4 / 2	93%
Parietal	58	6	4 / 2	91%
Occipital	31	1	1 / 0	97%
Other	7	5	0 / 5	58%

Table 5: Variables More / Less Associated with Cognition than the Canonical Function

Variables More Associated With Cognition than the BANCC	Variables Less Associated with Cognition than the BANCC
Biofactors	*Biofactors*
Antisaccade Biofactor	Paired Stimulus Ongoing HF
	Oddball Ongoing HF
Whole Lobe Volumes	P300 Complex
Left Frontal Volume	Latency Biofactor
Right Frontal Volume	IEA Biofactor
Left Temporal Volume	
Right Temporal Volume	*Thalamic Nuclei*
Left Parietal Volume	Left CL
Right Parietal Volume	Left CD
	Right CL
Lobe Subregion Volumes	Right LD
Left Lateral Orbitofrontal Volume	Left Medial Nucleus
Left Inferior Temporal Volume	Right Medical Nucleus
Right Middle Temporal Volume	
Left Postcentral Volume	*Hypothalamic Subnuclei*

Variables More Associated With Cognition than the BANCC	Variables Less Associated with Cognition than the BANCC
Left Superior Parietal Volume Right Lateral Occipital Volume	Left Anterior Inferior Right Anterior Inferior Left Anterior Superior Right Anterior Superior *Lobe Subregion Thicknesses* Right Rostral Anterior Cingulate Thickness Left Caudal Anterior Cingulate Thickness Right Caudal Anterior Cingulate Thickness Left Entorhinal Thickness Right Entorhinal Thickness Left Pericalcarine Thickness Right Pericalcarine Thickness *Other* Left Lateral Ventricle Right Lateral Ventricle Third Ventricle Fourth Ventricle

Variables More Associated With Cognition than the BANCC	Variables Less Associated with Cognition than the BANCC
	White Matter Hypointensities

Table 6: Medications Characteristics by DSM

Characteristic	Overall n =1459	Schizophrenia n = 579	Schizoaffective n = 434	Bipolar n = 424
Medication Status (%)				
Not Taking Medications	67 (4.6%)	25 (4.3%)	19 (4.3%)	22 (5.2%)
Taking Medications	1376 (94.3%)	545 (94%)	414 (95.4%)	399 (94.1%)
Mean Medication Count (SD)	4.69 (3.26)	4.27 (2.78)	5.04 (3.53)	4.90 (3.48)
Mean Psychotropic Medication Count (SD)	2.80 (1.54)	2.48 (1.38)	3.03 (1.54)	3.00 (1.68)
Psychotropics (%)	1324 (90.7%)	526 (90.8%)	395 (91.0%)	387 (91.3%)
Antipsychotics (%)	1172 (80.3%)	502 (86.7%)	356 (82.0%)	302 (71.2%)
1st Generation Antipsychotics (%)	161 (11.0%)	86 (14.9%)	54 (12.4%)	18 (4.2%)
2nd Generation Antipsychotics (%)	1050 (72.0%)	438 (75.6%)	316 (72.8%)	286 (67.4%)
Antidepressants (%)	670 (45.9%)	240 (41.5%)	232 (53.5%)	189 (44.6%)
Tricyclics (%)	24 (1.6%)	7 (1.2%)	5 (1.2%)	11 (2.6%)
SSRIs (%)	455 (31.2%)	174 (30.0%)	169 (38.9%)	104 (24.5%)
Other Antidepressants (%)	281 (19.3%)	87 (15.0%)	88 (20.3%)	100 (23.6%)
Mood Stabilizers (%)	635 (43.5%)	124 (21.4%)	213 (49.1%)	291 (68.6%)
Lithium (%)	187 (12.8%)	30 (5.2%)	46 (10.6%)	108 (25.4%)
Anticonvulsants (%)	483 (33.1%)	95 (16.4%)	183 (42.2%)	201 (47.4%)
Anxiolytics/Sedatives/Hypnotics (%)	351 (24.1%)	111 (19.2%)	106 (24.4%)	130 (30.7%)
Anticholinergics (%)	198 (13.6%)	110 (19.0%)	58 (13.4%)	28 (6.6%)
Centrally Active Medications (%)	68 (4.7%)	22 (3.8%)	21 (4.8%)	22 (5.2%)
Stimulants (%)	76 (5.2%)	18 (3.1%)	20 (4.6%)	37 (8.7%)
Analgesics (%)	292 (20.0%)	103 (17.8%)	92 (21.2%)	94 (22.2%)
Mean CPZ Equivalent Daily Dose (SD)	521.47 (764.12)	580.70 (759.11)	565.16(919.42)	352.55 (362.91)

Table 7. Medications Characteristics by Biotype

Characteristic	Overall n = 1459	Biotype-1 n = 481	Biotype-2 n = 483	Biotype-3 n = 476
Medication Status (%)				
Not Taking Medications	67 (4.6%)	22 (4.6%)	18 (3.7%)	26 (5.5%)
Taking Medications	1376 (94.3%)	449 (93.3%)	459 (95.0%)	449 (94.3%)
Mean Medication Count (SD)	4.69 (3.26)	4.73 (3.30)	4.93 (3.41)	4.42 (3.01)
Mean Psychotropic Medication Count (SD)	2.80 (1.54)	2.81(1.58)	2.83 (1.54)	2.76 (1.52)
Psychotropics (%)	1324 (90.7%)	439 (91.3%)	439 (90.9%)	429 (90.1%)
Antipsychotics (%)	1172 (80.3%)	401 (83.4%)	404 (83.6%)	354 (74.4%)
1st Generation Antipsychotics (%)	161 (11.0%)	52 (10.8%)	66 (13.7%)	40 (8.4%)
2nd Generation Antipsychotics (%)	1050 (72.0%)	360 (74.8%)	354 (73.3%)	325 (68.3%)
Antidepressants (%)	670 (45.9%)	221 (45.9%)	211 (43.7%)	229 (48.1%)
Tricyclics (%)	24 (1.6%)	4 (0.8%)	9 (1.9%)	10 (2.1%)
SSRIs (%)	455 (31.2%)	147 (30.6%)	153 (31.7%)	147 (30.9%)
Other Antidepressants (%)	281 (19.3%)	99 (20.6%)	81 (16.8%)	95 (20.0%)
Mood Stabilizers (%)	635 (43.5%)	208 (43.2%)	184 (38.1%)	235 (49.4%)
Lithium (%)	187 (12.8%)	53 (11.2%)	69 (14.3%)	62 (13.0%)
Anticonvulsants (%)	483 (33.1%)	166 (34.5%)	129 (26.7%)	183 (38.4%)
Anxiolytics/Sedatives/Hypnotics (%)	351 (24.1%)	107 (22.2%)	130 (26.9%)	110 (23.1%)
Anticholinergics (%)	198 (13.6%)	68 (14.1%)	78 (16.1%)	50 (10.5%)
Centrally Active Medications (%)	68 (4.7%)	18 (3.7%)	24 (5.0%)	23 (4.8%)
Stimulants (%)	76 (5.2%)	20 (4.2%)	21 (4.3%)	34 (7.1%)
Analgesics (%)	292 (20.0%)	82 (17.0%)	108 (22.4%)	98 (20.6%)
Mean CPZ Equivalent Daily Dose (SD)	521.47 (764.12)	522.73 (795.39)	553.08 (684.56)	467.08 (748.97)

Table 8. Demographics by DSM

Characteristic	Schizophrenia n = 579	Schizoaffective n = 434	Bipolar n = 424
Mean Age (SD)	37.63 (12.45)	38.77 (11.65)	36.52 (12.30)
Sex (%)			
Male	370 (64.1%)	186 (42.9%)	165 (38.9%)
Female	2 (36.3%)	248 (57.1%)	259 (61.1%)
Ethnicity (%)			
Not Hispanic	525 (90.7%)	377 (86.9%)	373 (88.0%)
Hispanic	52 (9.0%)	56 (12.9%)	51 (12.0%)
Race (%)			
Black	294 (50.8%)	177 (40.8%)	94 (22.2%)
American Indian	3 (0.5%)	2 (0.5%)	2 (0.4%)
Asian	23 (4.0%)	9 (2.1%)	9 (2.1%)
White	215 (37.1%)	201 (46.3%)	294 (69.3%)
Multiracial	26 (4.5%)	32 (7.4%)	14 (3.3%)
Hawaiian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)
Other	18 (3.1%)	13 (2.5%)	11 (2.6%)
Mean Global Functioning (SD)	49.55 (12.07)	51.18 (11.84)	58.8 (12.7)
Mean Proband SES (SD)	51.82 (13.74)	48.17 (13.85)	42.20 (14.59)

Characteristic	Schizophrenia n = 579	Schizoaffective n = 434	Bipolar n = 424
Mean Family SES (SD)	43.94 (16.3)	43.81 (16.21)	38.25 (15.73)

Table 9. Demographics by Biotype

Characteristic	Biotype-1 n = 478	Biotype-2 n = 483	Biotype-3 n = 476
Mean Age (SD)	38.06(12.35)	39.19 (11.66)	35.76 (12.3)
Sex (%)			
Male	266 (55.3%)	212 (43.9%)	243 (51.1%)
Female	212 (44.1%)	271 (56.1%)	233 (48.9%)
Ethnicity (%)			
Not Hispanic	420 (87.3%)	426 (88.2%)	429 (90.1%)
Hispanic	56 (11.6%)	56 (11.6%)	47 (9.9%)
Race (%)			
Black	241 (50.1%)	207 (42.9%)	117 (24.6%)
American Indian	5 (1.0%)	1 (0.2%)	1 (0.2%)
Asian	18 (3.7%)	7 (1.4%)	16 (3.4%)
White	179 (37.2%)	230 (47.6%)	301 (63.2%)
Multiracial	22 (4.6%)	25 (5.2%)	25 (5.3%)
Hawaiian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)
Other	13 (2.7%)	13 (2.7%)	16 (3.2%)
Mean Global Functioning (SD)	51.56 (12.2)	50.61 (12.05)	56.27 (13.4)
Mean Proband SES (SD)	50.49 (13.84)	49.37 (14.02)	43.66 (14.95)

Characteristic	Biotype-1 n = 478	Biotype-2 n = 483	Biotype-3 n = 476
Mean Family SES (SD)	44.36 (16.08)	44.23 (15.86)	38.10 (16.06)

Table 10. Clinical Characteristics by DSM (Means and SDs)

Characteristic	Overall n = 1437	Schizophrenia n = 579	Schizoaffective n = 434	Bipolar n = 424
Young Mania Scale	7.77 (7.42)	7.19 (6.84)	9.19 (7.71)	7.04 (7.65)
Montgomery-Asberg Depression Scale	11.28 (9.95)	8.67 (8.52)	14.22 (10.41)	11.79 (10.39)
Schizo-Bipolar Scale	5.17 (2.90)	7.92 (1.04)	5.11 (1.37)	1.49 (1.18)
Birchwood Social Functioning Scale (SFS)	122.46 (24.90)	117.83 (23.56)	118.48 (25.38)	132.89 (23.45)
SFS Social Engagement/Withdrawal	10.51 (2.43)	10.54 (2.28)	9.97 (2.55)	11.01 (2.35)
SFS Interpersonal Communication	7.15 (1.86)	6.89 (1.91)	6.90 (1.91)	7.73(1.63)
SFS Independence- Competence	31.89 (6.27)	31.49 (6.63)	30.97 (6.40)	33.44 (5.33)
SFS Independence- Performance	32.43 (6.22)	31.38 (6.29)	32.34 (6.59)	33.71 (5.33)
SFS Recreation	18.94 (7.40)	17.98 (7.18)	18.48 (7.67)	20.73 (7.14)
SFS Prosocial	17.34 (9.84)	15.60 (9.30)	15.97(9.18)	21.16 (10.25)
SFS Occupation/Employment	4.79 (3.51)	4.50 (3.38)	4.29 (3.46)	5.76 (3.59)
Positive and Negative Syndrome Scale (PANSS)	62.96 (19.02)	65.68 (18.74)	66.95 (19.03)	55.34 (17.3)
PANSS Positive	16.14 (6.16)	17.00 (6.06)	17.82 (6.20)	13.17 (5.19)
PANSS Negative	15.19 (6.16)	16.83 (6.24)	15.56 (6.10)	12.71 (5.30)
PANSS General	31.64 (9.47)	31.86 (9.5)	33.58 (9.42)	29.44 (9.12)

Table 11. Clinical Characteristics by Biotype (Means and SDs)

Characteristic	Overall n =	Biotype-1 n = 481	Biotype-2 n = 483	Biotype-3 n = 476
Young Mania Scale	7.77 (7.42)	7.68 (7.34)	8.37 (7.69)	7.28 (7.23)
Montgomery-Asberg Depression Scale	11.28 (9.95)	11.58 (10.40)	11.31 (10.00)	11.02 (9.52)
Schizo-Bipolar Scale	5.17 (2.90)	5.41 (2.79)	5.58 (2.88)	4.48 (2.93)
Birchwood Social Functioning Scale (SFS)	122.46 (24.90)	120.12 (24.39)	118.61 (23.85)	128.80 (25.54)
SFS Social Engagement/Withdrawal	10.51 (2.43)	10.49 (2.48)	10.47 (2.41)	10.57 (2.36)
SFS Interpersonal Communication	7.15 (1.86)	7.04 (1.82)	6.95 (1.92)	7.45 (1.83)
SFS Independence- Competence	31.89 (6.27)	32.05 (6.30)	31.13 (6.18)	32.60 (6.29)
SFS Independence- Performance	32.43 (6.22)	31.81 (6.57)	32.20 (6.00)	33.12 (6.07)
SFS Recreation	18.94 (7.40)	18.47 (7.35)	18.11 (7.50)	20.27 (7.19)
SFS Prosocial	17.34 (9.84)	15.94 (9.42)	16.39 (9.55)	19.69 (10.16)
SFS Occupation/Employment	4.79 (3.51)	4.51 (3.45)	4.30 (3.37)	5.61 (3.60)
Positive and Negative Syndrome Scale (PANSS)	62.96 (19.02)	63.04 (18.98)	66.64 (18.52)	59.45 (19.08)
PANSS Positive	16.14 (6.16)	16.7 (6.19)	17.47 (6.12)	14.78 (5.93)
PANSS Negative	15.19 (6.16)	15.47 (6.14)	16.24 (6.29)	13.97 (5.87)
PANSS General	31.64 (9.47)	31.42 (9.53)	32.95 (9.27)	30.67 (9.57)

Table 12. Complete List of MRI Variables

Structure Volumes	*Structure Areas*	*Structure Thicknesses*	*Structure Gyrifications*
Left bank ssts	*Left bank ssts*	*Left bank ssts*	*Left bank ssts*
Left caudal anterior cingulate	*Left caudal anterior cingulate*	*Left caudal anterior cingulate*	*Left caudal anterior cingulate*
Left caudal middle frontal	*Left caudal middle frontal*	*Left caudal middle frontal*	*Left caudal middle frontal*
Left cingulate	*Left cingulate*	*Left cingulate*	*Left cingulate*
Left cuneus	*Left cuneus*	*Left cuneus*	*Left cuneus*
Left entorhinal	*Left entorhinal*	*Left entorhinal*	*Left entorhinal*
Left frontal	*Left frontal*	*Left frontal*	*Left frontal*
Left frontal pole	*Left frontal pole*	*Left frontal pole*	*Left frontal pole*
Left fusiform	*Left fusiform*	*Left fusiform*	*Left fusiform*
Left inferior parietal	*Left inferior parietal*	*Left inferior parietal*	*Left inferior parietal*
Left inferior temporal	*Left inferior temporal*	*Left inferior temporal*	*Left inferior temporal*
Left insula	*Left insula*	*Left insula*	*Left insula*
Left isthmus cingulate	*Left isthmus cingulate*	*Left isthmus cingulate*	*Left isthmus cingulate*
Left lateral occipital	*Left lateral occipital*	*Left lateral occipital*	*Left lateral occipital*
Left lateral orbitofrontal	*Left lateral orbitofrontal*	*Left lateral orbitofrontal*	*Left lateral orbitofrontal*
Left lingual	*Left lingual*	*Left lingual*	*Left lingual*
Left medial orbitofrontal	*Left medial orbitofrontal*	*Left mean thickness*	*Left medial orbitofrontal*
Left middle temporal	*Left middle temporal*	*Left medial orbitofrontal*	*Left middle temporal*
Left occipital	*Left occipital*	*Left middle temporal*	*Left occipital*
Left paracentral	*Left paracentral*	*Left occipital*	*Left paracentral*
Left parahippocampal	*Left parahippocampal*	*Left paracentral*	*Left parahippocampal*
Left parietal	*Left parietal*	*Left parahippocampal*	*Left parietal*
Left pars opercularis	*Left pars opercularis*	*Left parietal*	*Left pars opercularis*
Left pars orbitalis	*Left pars orbitalis*	*Left pars opercularis*	*Left pars orbitalis*
Left pars triangularis	*Left pars triangularis*	*Left pars orbitalis*	*Left pars triangularis*
Left pericalcarine	*Left pericalcarine*	*Left pars triangularis*	*Left pericalcarine*
Left postcentral	*Left postcentral*	*Left pericalcarine*	*Left postcentral*
Left posterior cingulate	*Left posterior cingulate*	*Left postcentral*	*Left posterior cingulate*
Left precentral	*Left precentral*	*Left posterior cingulate*	*Left precentral*
Left precuneus	*Left precuneus*	*Left precentral*	*Left precuneus*
Left rostral anterior cingulate	*Left rostral anterior cingulate*	*Left precuneus*	*Left rostral anterior cingulate*
Left rostral middle frontal	*Left rostral middle frontal*	*Left rostral anterior cingulate*	*Left rostral middle frontal*
Left superior frontal	*Left superior frontal*	*Left rostral middle frontal*	*Left superior frontal*
Left superior parietal	*Left superior parietal*	*Left superior frontal*	*Left superior parietal*
Left superior temporal	*Left superior temporal*	*Left superior parietal*	*Left superior temporal*
Left supramarginal	*Left supramarginal*	*Left superior temporal*	*Left supramarginal*
Left temporal	*Left temporal*	*Left supramarginal*	*Left temporal*
Left temporal pole	*Left temporal pole*	*Left temporal*	*Left temporal pole*
Left transverse temporal	*Left transverse temporal*	*Left temporal pole*	*Left transverse temporal*
Right bankssts	*Right bankssts*	*Left transverse temporal*	*Right bankssts*
Right caudal anterior cingulate		*Right bankssts*	

Right caudal middle frontal
Right cingulate
Right cuneus
Right entorhinal
Right frontal
Right frontal pole
Right fusiform
Right inferior parietal
Right inferior temporal
Right insula
Right isthmus cingulate
Right lateral occipital
Right lateral orbitofrontal
Right lingual
Right medial orbitofrontal
Right middle temporal
Right occipital
Right paracentral
Right parahippocampal
Right parietal
Right pars opercularis
Right pars orbitalis
Right pars triangularis
Right pericalcarine
Right postcentral
Right posterior cingulate
Right precentral
Right precuneus
Right rostral anterior cingulate
Right rostral middle frontal
Right superior frontal
Right superior parietal
Right superior temporal
Right supramarginal
Right temporal
Right temporal pole
Right transverse temporal

Right caudal anterior cingulate
Right caudal middle frontal
Right cingulate
Right cuneus
Right entorhinal
Right frontal
Right frontal pole
Right fusiform
Right inferior parietal
Right inferior temporal
Right insula
Right isthmus cingulate
Right lateral occipital
Right lateral orbitofrontal
Right lingual
Right medial orbitofrontal
Right middle temporal
Right occipital
Right paracentral
Right parahippocampal
Right parietal
Right pars opercularis
Right pars orbitalis
Right pars triangularis
Right pericalcarine
Right postcentral
Right posterior cingulate
Right precentral
Right precuneus
Right rostral anterior cingulate
Right rostral middle frontal
Right superior frontal
Right superior parietal
Right superior temporal
Right supramarginal
Right temporal
Right temporal pole
Right transverse temporal

Right caudal anterior cingulate
Right caudal middle frontal
Right cingulate
Right cuneus
Right entorhinal
Right frontal
Right frontal pole
Right fusiform
Right inferior parietal
Right inferior temporal
Right insula
Right isthmus cingulate
Right lateral occipital
Right lateral orbitofrontal
Right lingual
Right mean thickness
Right medial orbitofrontal
Right middle temporal
Right occipital
Right paracentral
Right parahippocampal
Right parietal
Right pars opercularis
Right pars orbitalis
Right pars triangularis
Right pericalcarine
Right postcentral
Right posterior cingulate
Right precentral
Right precuneus
Right rostral anterior cingulate
Right rostral middle frontal
Right superior frontal
Right superior parietal
Right superior temporal
Right supramarginal
Right temporal
Right temporal pole
Right transverse temporal

Right caudal anterior cingulate
Right caudal middle frontal
Right cingulate
Right cuneus
Right entorhinal
Right frontal
Right frontal pole
Right fusiform
Right inferior parietal
Right inferior temporal
Right insula
Right isthmus cingulate
Right lateral occipital
Right lateral orbitofrontal
Right lingual
Right medial orbitofrontal
Right middle temporal
Right occipital
Right paracentral
Right parahippocampal
Right parietal
Right pars opercularis
Right pars orbitalis
Right pars triangularis
Right pericalcarine
Right postcentral
Right posterior cingulate
Right precentral
Right precuneus
Right rostral anterior cingulate
Right rostral middle frontal
Right superior frontal
Right superior parietal
Right superior temporal
Right supramarginal
Right temporal
Right temporal pole
Right transverse temporal

Subcortical Structures

Left accessory basal nucleus

Left basal nucleus

Left CA1

Left CA3

Left CA4

Left caudate

Left GC ML DG of the hippocampus

Left hippocampal tail

Left pallidum

Left putamen

Left subiculum

Left whole amygdala

Left whole hippocampus

Left whole hypothalamus

Left whole thalamus

Right accessory basal nucleus

Right basal nucleus

Right CA1

Right CA3

Right CA4

Right caudate

Left GC ML DG of the hippocampus

Right hippocampal tail

Right pallidum

Right putamen

Right subiculum

Right whole amygdala

Right whole hippocampus

Right whole hypothalamus

Right whole thalamus

Thalamic Subregions

Left AV (anteroventral)

Left CeM (centromedian)

Left CL (central lateral)

Left CM (central medial)

Left Lateral Nucleus

Left LD (laterodorsal)

Left LGN (lateral geniculate nucleus)

Left LP (lateral posterior)

Left L Sg (suprageniculate-limitans complex)

Left Medial Nucleus

Left MDl (mediodorsal lateral parvocellular)

Left MDm (mediodorsal medial magnocellular)

Left MGN (medial geniculate nucleus)

Left MV Re (medial ventral reuniens)

Left Pc (paracentral)

Left Pf (parafascicular)

Left PuA (pulvinar anterior)

Left PuI (pulvinar inferior)

Left PuL (pulvinar lateral)

Left PuM (pulvinar medial)

Left VA (ventral anterior)

Left VAmc (ventral anterior magnocellular)

Left VLa (ventral lateral anterior)

Left VLp (ventral lateral posterior)

Left VM (ventromedial)

Left VPL (ventral posterolateral)

Right AV (anteroventral)

Right CeM (centromedian)

Right CL (central lateral)

Right CM (central medial)

Right Lateral Nucleus

Right LD (laterodorsal)

Right LGN (lateral geniculate nucleus)

Right LP (lateral posterior)

Ventricular Volumes

Left lateral ventricle

Right lateral ventricle

3rd ventricle

4th ventricle

Hypothalamus Subnuclei

Left Anterior Inferior

Left Anterior Superior

Left Posterior

Right Anterior Inferior

Right Anterior Superior

Right Posterior

Other

Left Molecular Layer HP

Left Tubular Inferior

Left Tubular Superior

Right Molecular Layer HP

Right Tubular Inferior

Right Superior

Total Intercranial Volume

White Matter Hypointensities

Right L Sg (suprageniculate-limitans complex)

Right Medial Nucleus

Right MDl (mediodorsal lateral parvocellular)

Right MDm (mediodorsal medial magnocellular)

Right MGN (medial geniculate nucleus)

Right MV Re (medial ventral reuniens)

Right Pc (paracentral)

Right Pf (parafascicular)

Right PuA (pulvinar anterior)

Right PuI (pulvinar inferior)

Right PuL (pulvinar lateral)

Right PuM (pulvinar medial)

Right VA (ventral anterior)

Right VAmc (ventral anterior magnocellular)

Right VLa (ventral lateral anterior)

Right VLp (ventral lateral posterior)

Right VM (ventromedial)

Right VPL (ventral posterolateral)

Table 13. Component 1 for PCA of Variables Deviating High

Component Matrix	
	Component
	1
Right Temporal Volume	0.954
Left Temporal Volume	0.953
Left Parietal Volume	0.943
Right Frontal Volume	0.939
Left Frontal Volume	0.937
Right Parietal Volume	0.932
Right Midtemporal Volume	0.878
Left Lateral Orbitofrontal Volume	0.871
Left Inferior Temporal Volume	0.838
Left Postcentral Volume	0.817
Left Superiorparietal Volume	0.789
Right Lateral Occipital Volume	0.757
Antisaccade Biofactor	0.18

Table 14. Components 1-8 for PCA of Variables Deviating Low

Structure Matrix								
	Component							
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Right Lateral Ventricle	0.909	0.15	<0.1	0.103	0.189	<0.1	<0.1	<0.1
Left Lateral Ventricle	0.904	0.157	<0.1	<0.1	0.211	<0.1	<0.1	<0.1
Third Ventricle	0.856	0.218	<0.1	<0.1	<0.1	<0.1	<0.1	-0.123
White Matter Hypointensities	-0.546	<0.1	0.104	<0.1	-0.174	-0.14	<0.1	<0.1
4th Ventricle	0.531	0.112	<0.1	<0.1	-0.154	<0.1	-0.103	-0.254
Right CL of the Thalamus	<0.1	0.81	<0.1	0.134	<0.1	0.109	<0.1	0.26
Right LC of the Thalamus	0.283	0.807	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Left LD of the Thalamus	0.358	0.793	<0.1	<0.1	<0.1	0.122	<0.1	0.112
Left CL of the Thalamus	<0.1	0.791	<0.1	<0.1	<0.1	0.155	<0.1	0.281
Paired Stimulus Ongoing Biofactor	<0.1	<0.1	0.901	<0.1	<0.1	<0.1	<0.1	<0.1
IEA Biofactor	<0.1	<0.1	0.87	<0.1	<0.1	<0.1	<0.1	<0.1
Oddball Ongoing Biofactor	<0.1	<0.1	0.852	<0.1	<0.1	<0.1	<0.1	<0.1
Left Anterior Superior Subnucleus of the Hypothalamus	<0.1	<0.1	<0.1	0.776	<0.1	<0.1	0.108	0.241
Right Anterior Superior Subnucleus of the Hypothalamus	<0.1	<0.1	<0.1	0.759	<0.1	<0.1	0.103	0.233
Right Anterior Inferior Subnucleus of the Hypothalamus	<0.1	<0.1	<0.1	0.711	<0.1	<0.1	<0.1	<0.1
Left Anterior Inferior Subnucleus of the Hypothalamus	<0.1	<0.1	<0.1	0.7	<0.1	<0.1	<0.1	<0.1
Right Caudal Anterior Cingulate Thickenss	0.238	<0.1	<0.1	<0.1	0.816	0.168	<0.1	0.104
Right Rostral Anterior Cingulate Thickness	<0.1	<0.1	<0.1	<0.1	0.745	0.139	0.196	<0.1
Right Frontal Pole Gyrification	0.168	<0.1	<0.1	<0.1	0.738	0.15	<0.1	<0.1
Right Pericalcarine Thickness	<0.1	<0.1	<0.1	<0.1	0.186	0.904	0.108	0.11
Left Pericalcarine Thickness	<0.1	0.142	<0.1	<0.1	0.182	0.898	<0.1	<0.1
Left Entorhinal Thickness	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.864	<0.1

Right Entorhinal Thickness	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.855	<0.1
Left Medial Nucleus of the Thalamus	<0.1	0.247	<0.1	0.135	<0.1	<0.1	<0.1	0.822
Right Medial Nucleus of the Thalamus	<0.1	0.179	<0.1	0.185	<0.1	<0.1	<0.1	0.821
Latency Biofactor	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
P300 Biofactor	<0.1	<0.1	0.297	<0.1	<0.1	<0.1	<0.1	<0.1

Figure 1: Plot of Predictors Over Cognitive Performance by Group

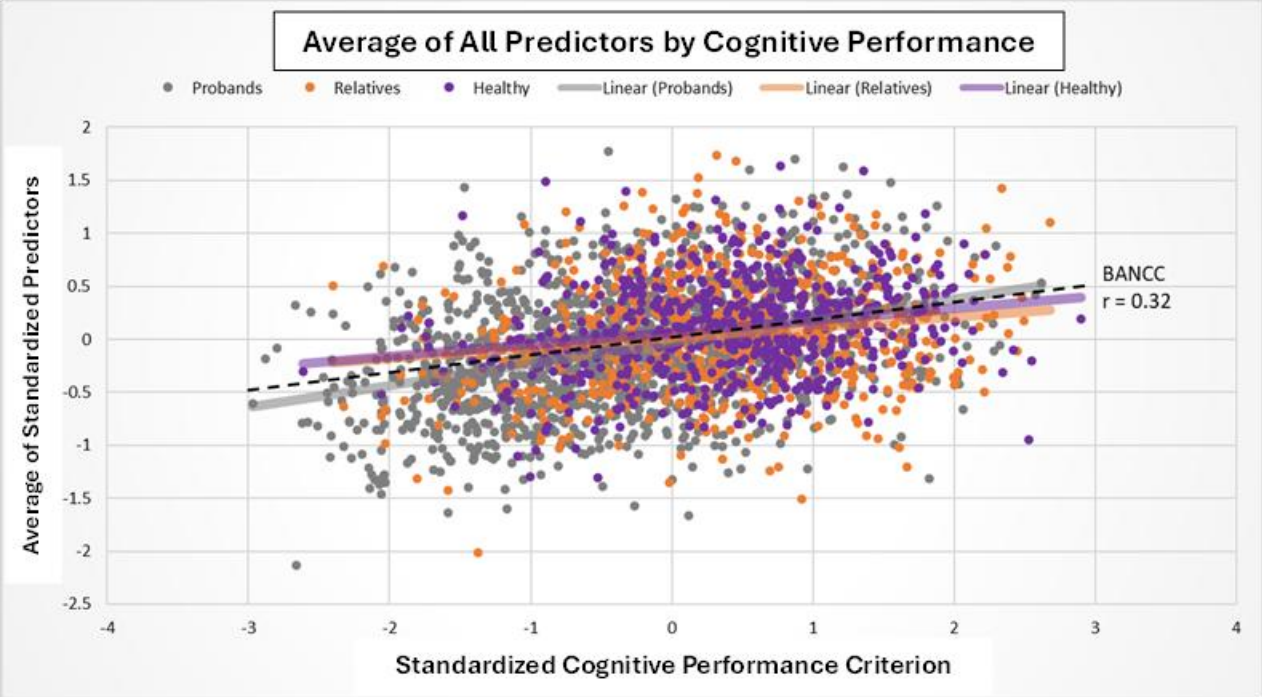

Figure 1: This plot shows a breakdown of the relationship between cognitive performance (the "criterion") and an average of all predictor variables for each subject. Proband (Psychosis) subjects, and their group slope, are in grey, while First-Degree Relatives are in Orange, and Health Controls are in Purple. The overall BANCC slope is outlined in a black dashed line, with a slope of y = .19x + .05, and a Pearson's r value of .05.

Figure 2: Plot of Variables Deviating from Canonical BANCC Function

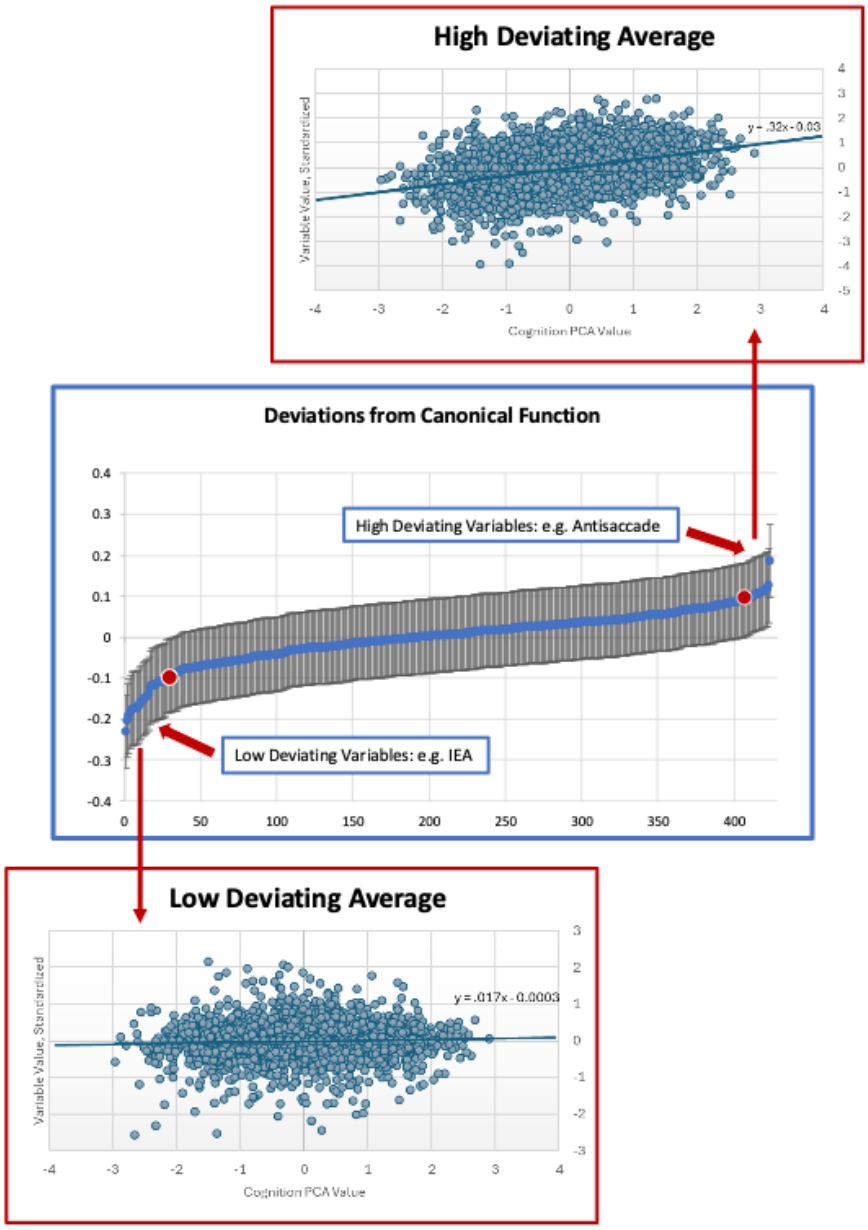

Figure 2: This image shows a caterpillar plot of the mean deviation of all variables in blue dots, with 99.9% Bonferroni-adjusted Confidence Intervals. Red dots indicate the 0.1 cutoff determined to encapsulate the function. Variables below the first red dot, with slopes less related to cognition than the BANCC, have subject averages described in the bottom plot, and produce an average slope of .017x + .0003. Variables above the second red dot, with slopes more related to cognition than the BANCC, have subject averages described in the top plot, and produce an average slope of .32x - 0.03.

Figure 3: Discriminant Analysis Outcomes

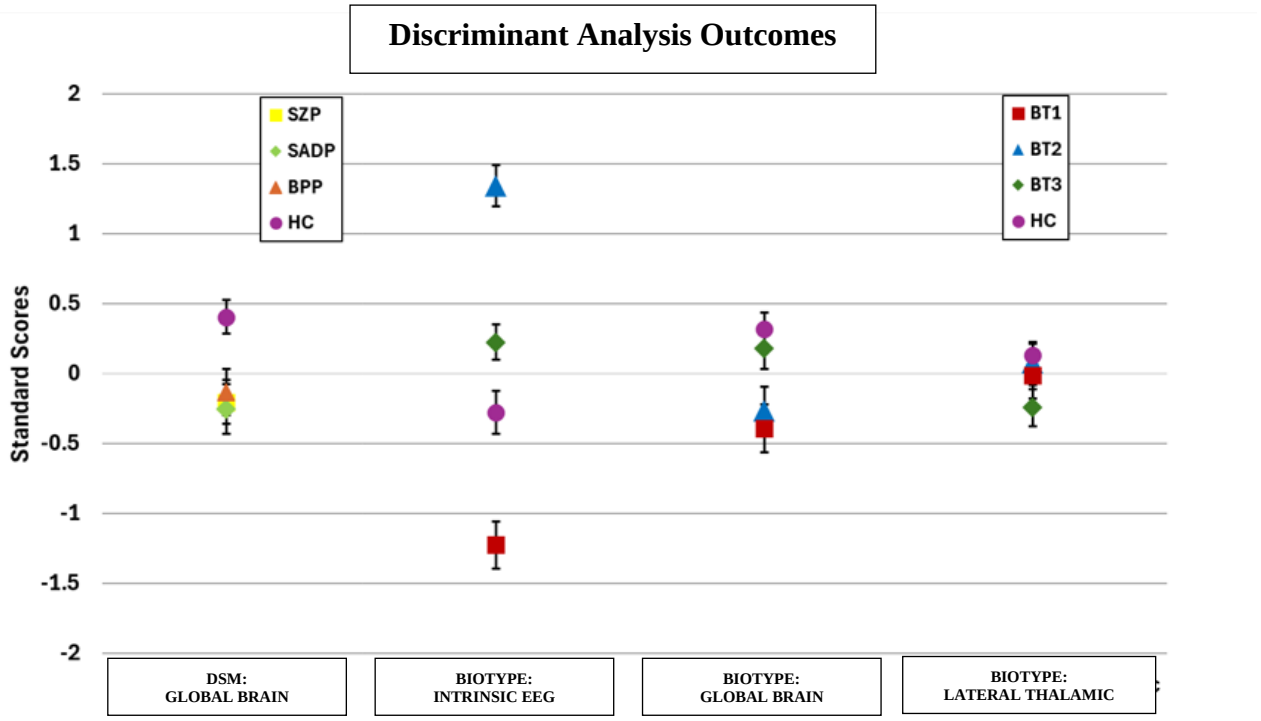

Figure 3: This plot illustrates the four significant variables generated by the discriminant analysis, their subgroups' scores and 95% Confidence Intervals around each mean score. First, for the discriminant analysis by DSM diagnosis- one variable reflecting global brain volume, broken down into Schizophrenia (SZP), Schizoaffective (SADP), Bipolar with Psychosis (BPP), and Health Controls. Next, three variables from the analysis by biotype- one variable reflecting intrinsic EEG measures, one variable reflecting global brain volume, and one variable reflecting lateral thalamic volume. These are broken down between Biotypes 1, 2, 3, and Healthy Controls.