

ASSOCIATIONS OF SOCIAL AND GENETIC BACKGROUND VARIABLES TO NEURO- COGNITIVE BIOMARKERS OF PSYCHOSIS

by

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(Under the Direction of Brett Clementz)

ABSTRACT

Clinical psychosis diagnoses depend on patient and informant reports, but such evaluations are susceptible to bias. Diagnoses using laboratory tests are considered more objective, although social disadvantages alter brain functions related to psychosis. I probed relationships of SES, race/ethnicity, and genetic background to 11 integrated laboratory bio-factors that are associated with psychosis and distinguish B-SNIP psychosis Biotypes. A series of analyses evaluated relationships of social factors and ancestry-related genetic background on those bio-factors: (i) canonical correlation revealed that SES and race (a social construct) are moderately associated ($r=.305$) with cognitive performance and measures of brain physiology (prominently ERP magnitudes); genetic background neither significantly added to nor altered the structure of those associations; (ii) regression models illustrated that cognitive performance, intrinsic brain activity, and ERP magnitudes are substantially to modestly predicted by SES/race/genetic background, with SES/race accounting for the most variance on cognitive performance (approximately 25%); (iii) regardless of including SES/race in differential diagnosis models, group differences between psychosis Biotypes were largely (85%) preserved on bio-factor scores. These outcomes illustrate that social factors are associated with psychosis-related

laboratory tests. Nevertheless, SES/race did not substantially modify differential diagnosis of psychosis Biotypes. Using laboratory tests for psychosis differential diagnosis may facilitate the usefulness of stratification approaches, aid investigations of psychosis neurobiology, and improve treatment selections for all persons suffering with idiopathic psychosis.

INDEX WORDS: psychosis; Schizophrenia; race; SES; electrophysiology; neurophysiology; neuropsychiatry; epidemiology

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1. INTRODUCTION

Utilizing clinical phenomenology alone to diagnose major psychiatric conditions has proven to be a very limiting feature of the field of psychiatry. The vast neurobiological differences across individuals with serious psychiatric conditions make the trial-and-error approach of psychiatric treatment the only reasonable option for clinicians and their patients, often prolonging those patients' struggles. The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) is a consortium of scientists with the common goal of utilizing laboratory tests to aid in determining individual treatment plans and improving outcomes for patients with idiopathic psychosis. The consortium used neurobiological markers to identify subtypes of psychosis with replicable neurobiological characteristics to yield psychosis "Biotypes." Biotypes, which are subgroups based on biological phenotypes (Clementz et al., 2016), were acquired using an array of laboratory tasks that assess neuro-cognitive performance and perceptual brain function. The data illustrated that individuals within one of three psychotic diagnostic groups as defined by the Diagnostic and Statistical Manual for Mental Disorders (DSM) – schizophrenia, schizoaffective disorder, and psychotic bipolar disorder – varied greatly in their neurobiological markers. By identifying biomarker features across individuals with diagnoses of one of these conditions, the B-SNIP consortium found three clearly defined groups with homogenous neurophysiology; however, these subgroups did not fall in line with the participants' clinical DSM diagnoses. Biotype 1 (B1), Biotype 2 (B2), and Biotype 3 (B3) could be distinguished from each other by observing brain anatomy, brain electrophysiology, cognitive performance, and ocular motion (Clementz et al., 2020). These biomarkers suggest biological homogeneity within psychosis Biotype groups that DSM syndrome diagnostics do not capture (Tamminga et al., 2014). B-SNIP psychosis Biotypes

have characteristic biomarker patterns, replicate, cross-validate, and yield treatment targets not derivable from any other approach to psychosis diagnosis (Clementz et al., 2020). Researchers suspect that individuals receiving the same psychosis-causing diagnoses per the DSM differ significantly from one another neurobiologically, and categorizing psychosis groups using Biotypes may give us a better understanding of how these idiopathic psychosis cases should be treated.

The current diagnostic “gold standard” for serious psychiatric disorders is doing patients with psychosis a disservice overall, but may be affecting some groups even more so than others. Epidemiological research has identified sociodemographic features that influence the development of psychiatric disorders, including race and socioeconomic status. Two epidemiologic studies examined Black-White differences in the treated incidence of schizophrenia, and both found higher rates among Black people (Akinhanmi et al., 2018; Bresnahan et al., 2007; Schwartz & Blankenship, 2014). Exploration of these factors may help elucidate further differences between group and disease outcomes. Addressing sociodemographic factors in psychosis may lead to improved treatment plans utilizing antipsychotic drugs, reducing the burden of treatment-resistant psychosis, as well as improving clinical outcomes, ultimately enhancing the quality of life for those who are affected by these severe psychiatric conditions.

Socioeconomic (SES) deficits are features commonly associated with schizophrenia spectrum diagnoses. It is known that factors such as living environment, parental socioeconomic status, and accessibility to healthcare influence outcomes in psychiatric patients (Misra et al., 2022), and that SES and ethno-racial groups are differentially exposed to modifiers of disease risk (Anglin et al., 2023; van der Ven & Susser, 2023). Research in human neuroscience has yielded results associating growing up in low SES with substantially impaired psychological well-being

and cognitive and emotional development (Hackman, Farah, & Meaney, 2010). Kirchner et al. (2020) investigated the role of socioeconomic status (SES) in individuals' brain structure and found an association between SES and decreased brain volume. Individuals with severe cognitive performance and social deficits are more likely to experience reduced neural reactivity when presented with emotional stimuli (Trotti et al., 2022), and individuals who receive a DSM diagnosis of schizophrenia tend to have particularly severe cognitive performance dysfunction and negative symptoms such as blunted affect and anhedonia (Saddock & Saddock, 2021). Treating all psychosis patients presenting the often assumed “telltale signs” of schizophrenia homogeneously may not be the appropriate pharmacological approach if these patients' neurobiology differ substantially. Further investigation into how SES affects the onset and severity of psychosis cases is a significant and critical gap to fill within the B-SNIP literature.

In the U.S., Black individuals experience health disparities and social disadvantage at a higher rate than do White individuals. The rate of schizophrenia diagnosis varies greatly by race, with Black individuals receiving a diagnosis at higher rates (Schwartz & Blankenship, 2014). We observe that the relationship between diagnosis and race is partially mediated by socioeconomic status, but SES does not fully explain this relationship; additional factors may be acting on this correlation such as racial trauma, cultural bias of clinicians, and a myriad of other stressors that disproportionately affect people of color and individuals with poor income-to-need ratios, variables that research knows to be confounding.

B-SNIP psychosis Biotypes were developed based on laboratory tests. Are biases related to socioeconomic or ethno-racial factors related to such laboratory-based psychosis diagnoses? Neuroscience research shows the effects of social disadvantage on multiple brain measures of relevance to psychosis. Lower SES is associated with less diverse educational opportunities (Hahn

& Truman, 2015), environmental exposures that influence cognitive development and performance (Bertola et al., 2021; Sheehy-Skeffington, 2020; Sosu & Schmidt, 2022; Yu et al., 2024), and may influence cellular biology via epigenetics (Turcotte et al., 2024). The effects of low family SES on one's neurobiology can extend beyond early life development (Tomassi et al., 2017). These effects disproportionately affect Black persons in the US, partially independent of SES (Delphin-Rittmon et al., 2015; Faber et al., 2023) and perhaps influence laboratory-based differential psychosis diagnosis.

Diagnosis aided by neurobiology may improve the objectivity of psychosis diagnosis and facilitate the stratification of patients into subgroups with specific treatment targets. Measures of brain structure and function are influenced by constitution, including genetics, but also may be influenced by the environment within which a person develops and lives. Social disadvantage may impact even laboratory-based diagnostic practices and clinical outcomes (Benjamin et al., 2024; Turcotte et al., 2024). SES disproportionately disadvantages certain racial and ethnic groups in the United States, so there can be a conflation of race (a social construct based on self-report and perception by others), ethnicity (shared culture), and SES (educational, occupational, and financial attainment), but each should be probed as contributors (Faber et al., 2023; Nagendra et al., 2020; Sarullo et al., 2024). The genetic background (cross-generational genetic similarity) upon which these sociodemographic and ethno-racial factors are manifested should also be considered.

This manuscript explores whether SES, self-identified race, ethnicity, and/or genetic background are related to laboratory measures used to investigate etiological and neurobiological correlates of psychosis. I used multiple analytical approaches to compare the relationship of different measures of social advantage/disadvantage to cognitive and physiological features that define psychosis Biotypes and are related to DSM-type psychosis diagnosis and tested whether

social characteristics account for or modify the ability to distinguish laboratory-based (B-SNIP Biotypes) or clinical (DSM-type) psychosis diagnoses.

2. METHOD

2.1 Subjects

Subject recruitment, interviews, and laboratory data collection were completed at B-SNIP sites([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). All interviews and laboratory data collections were completed at those locations. The Institutional Review Board at those institutions approved the projects; participants provided informed consent prior to involvement.

Clinically stable outpatients were administered the Structured Clinical Interview for DSM diagnosis (DSM-IV-TR;([American-Psychiatric-Association, 2000](#))). Psychosis cases were limited to schizophrenia, schizoaffective disorder, and bipolar I disorder with psychosis because these are diagnoses with the highest prevalence in most clinical settings. Healthy persons were administered the nonpatient version of the SCID. Participants were rated on the Birchwood Social Functioning([Birchwood et al., 1990](#)), Montgomery-Asberg Depression Rating([Montgomery & Asberg, 1979](#)), Positive and Negative Syndrome([Kay et al., 1987](#)), and Young Mania Rating ([Young et al., 1978](#)) scales.

Psychosis cases (a maximum n=1489 were available for this project) were drawn from academic and community mental health centers, small towns with large universities, large cities, inner cities, rural regions, affluent and less affluent areas. Healthy participants (a maximum n=685) were recruited from those same communities. Psychosis and healthy participants were not matched on propensity to access clinical care, nor on social or genetic background

characteristics to the populations from which they were recruited. This imposes limits on interpretation (see Discussion).

Data were collected on individual and family-of-origin socioeconomic status (SES; measured by the Hollingshead two-factor index, which incorporates level of education and occupational success; high scores indicate lower SES). Self-identified race and ethnicity were available for these participants. Social assignment based on others' perceptions and additional factors are important for understanding the relationships between race and health disparities(White et al., 2020), but such information was not available. Three self-identified race/ethnicity variables were constructed for subsequent analyses: Black (1) or not (0), Asian (1) or not (0), and Hispanic (1) or not (0), a customary approach when constructing dummy variables for multivariate models (Knapp, 1978) — the below analyses estimated their individual and combined contributions to the questions of interest. Table 2.1.1 shows demographic and clinical information by Biotype (Table 2.1.2 shows this information by DSM diagnosis). We previously showed that medications do not account for group differences on biomarkers(Clementz et al., 2022; Parker et al., 2024).

2.2 Genetic background quantification

Genotype imputation was done using Minimac4 on the Michigan Imputation Server, taking 1000 Genomes phase 3 v5 (hg19) mixed population as the reference panel with Eagle as the phasing algorithm (Das et al., 2016). Genetic markers were retained to have imputation quality metric $R^2 > 0.3$ (which removes $> 70\%$ of poorly imputed SNPs at the cost of $< 0.5\%$ well-imputed SNPs; Das et al., 2016), missingness $< 0.001\%$, MAF $> 1\%$, and HWE $P < 1E-5$. Individuals with genotype missingness > 0.05 or with Cryptic Relatedness 2nd degree or closer were filtered out using the KING program (Manichaikul et al., 2010). LD pruning was not done,

because of multiple ancestries. Genotype-based sex and heterozygosity rates were also checked for quality control. There were 10,321,126 total variants after quality control. As was described previously for B-SNIP data([Alliey-Rodriguez et al., 2019](#)), principal component analysis (PCA) was performed on genotypes of the individuals. The scree plot of this PCA identified three possibly useful genetic background components across individuals. The genetic principal components are dimensional scales and were used as such in subsequent analyses([Dauda et al., 2023](#); [Lewis et al., 2022](#)).

2.3 Bio-factor scores and Biotypes determination

Papers on the individual laboratory tasks provide data collection and analysis details([Ethridge et al., 2014](#); [Hill et al., 2013](#); [Huang et al., 2022](#); [Parker et al., 2020](#); [Parker et al., 2021](#)). Details of biomarker quantification and biotyping procedures are in [Clementz et al. \(2022\)](#) and [Parker et al. \(2024\)](#), including extensive supplementary methods. Laboratory measures used to obtain bio-factor scores (what we call integrated biomarker variables) were (i) the Brief Assessment of Cognition in Schizophrenia (BACS;([Keefe et al., 2004](#)), (ii) Stop-Signal Task (SST;([Lipszyc & Schachar, 2010](#)), (iii) pro- and anti-saccade tasks (saccades;([Hallett & Adams, 1980](#); [McDowell & Clementz, 2001](#)), (iv) auditory paired stimuli and oddball tasks (ERPs;([Freedman et al., 1987](#); [Polich, 2007](#)), and (v) the 9-10 second inter-pair interval of the paired stimuli task (intrinsic EEG activity or IEA;([Thomas et al., 2019](#)).

Following quantification of the tasks and paradigms, as described in relevant publications, PCA was performed within each laboratory measurement. This process produced 11 variables called bio-factors ([Clementz et al., 2022](#); [Parker et al., 2024](#)) — BACS, antisaccade, SST, intrinsic EEG activity, paired-stimuli ongoing activity, oddball ongoing activity, paired-stimuli ERPs, oddball ERPs, Frontal P300, paired-stimuli S2 response, and saccade latency.

These bio-factors were used to obtain B-SNIP psychosis Biotype designations via numerical taxonomy procedures described in previous B-SNIP papers([Clementz et al., 2022](#); [Parker et al., 2024](#)). Psychosis cases have a Biotype (Biotype-1, Biotype-2, or Biotype-3) and a DSM diagnosis (schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis).

2.4 Data Analyses

Three approaches were used to probe the relationships between SES-race-genetic background and bio-factor scores: (i) canonical correlation using all variables simultaneously, (ii) linear regressions between social/genetic background variables and individual bio-factors and mediation models to probe how race and SES mediate those relationships, and (iii) analysis of variance comparing the effects of social variables on differentiations of Biotype and DSM groups. Those procedures and their purposes are described below.

2.4.1 Canonical correlation. Canonical correlation (CCA) probed the bidirectional relationships between SES, self-identified race, ethnicity, and genetic background on one side of the equation to B-SNIP bio-factors on the other side of the equation¹ CCA identifies the relationship between two sets of variables by maximizing correlations between linear combinations of the sets, one on each side of the equation([Levine, 1977](#); [Wang et al., 2020](#)). CCA is the general procedure for investigating the relationship between two variable sets, and for which other parametric significance tests are special cases([Knapp, 1978](#)). CCA creates correlated pairs of latent variates. Each pair is independent (additional variate pairs are calculated

¹ The CCA models require every participant to have every measure, in this case every participant must have a value for 19 different variables. Rather than interpolating missing values for these analyses, we only included participants in the CCAs with complete data. This reduced the psychosis sample to 772 and the healthy sample to 395. Interpolating missing data, however, has no effect on the conclusions.

on the remainder after accounting for variance of the preceding variates) and composed of weighted sums of one variable set that maximally correlate with the weighted sums of the other variable set. Like PCA, interpretation of the latent variates is through the loadings of individual measures with the latent structure. The loadings are correlations of each individual variable in a set with that set's latent variate. This approach describes the association of each variable with its latent variate rather than interpreting the individual weights used to construct the latent variate(Levine, 1977).

Two CCAs were conducted: (i) using only SES (parental and participant separately) and self-identified race/ethnicity (Black or not, Asian or not, Hispanic or not), and (ii) another adding the first three genetic background PCA components to SES and self-identified race/ethnicity. This allowed for comparisons between component structures and canonical loadings both without and with genetic background information. On one side of the equation, the first CCA had 5 variables and the second CCA had 8 variables. Both CCAs had the 11 bio-factors on the other side of the equation.

The multivariate nature of CCA does not require multiple testing within a CCA analysis, although multiple testing across the two CCA analyses does and was accounted for by Bonferroni correction with the threshold for significance set at $p=.005$ (.01 divided by 2 CCA analyses). To evaluate the stability of the canonical variate structures, and any difference in component structures between the two CCA solutions, we implemented a jackknife procedure. We conducted analyses with a randomly selected 80% of the sample and repeated this procedure 10,000 times. We then computed the 99% confidence intervals across those samples for percent of variance accounted for by each CCA and for the component loadings to determine if adding

genetic background changed the variance accounted for or component structures of the bivariate relationships. Smaller confidence intervals also demonstrate the stability of the CCAs.

2.4.2 Linear Regression & Mediation Models. The CCAs describe the bi-directional relationships between two sets of variables. They do not describe the individual relationships between the SES, race, and genetic background and individual bio-factor scores. Based on the outcomes of the CCAs ([Wang et al., 2020](#)), regression models were constructed using the `lm()` function in R between SES/race/genetic background variables with beyond zero canonical loadings. These analyses describe the maximum shared variance between individual qualifying SES, self-identified race, and genetic background variables and the 11 individual bio-factors (see Table 3.2.1).

Mediation models tested whether genetic similarity has a direct relationship to bio-factor scores unaccounted for by socio-demographic variables. I used the Mediation functions in R to test these hypotheses. Models were constructed that maximized the direct relationship between genetic similarity PCs and each individual bio-factor, then two possible mediators were added: (i) one that maximized the relationship between personal and family SES and each bio-factor and (ii) one that maximized the relationship between self-identified race and each bio-factor. These models were then used to quantify the amount by which the direct relationship between genetic similarity and each individual bio-factor was mediated by socio-demographic information.

2.4.3 Analysis of Variance. The above analyses explore the relationships between social and genetic background information and bio-factors, but they do not assess how such relationships affect Biotype or DSM differentiations on the bio-factors. This is especially relevant for Biotypes, since the categories are created from the bio-factors. For every social variable that significantly contributed to bio-factor scores, we performed Biotype (Biotype-1,

Biotype-2, Biotype-3) by DSM (schizophrenia, schizoaffective, bipolar) ANOVAs. These models also tested for possible interactions between Biotype and DSM diagnostic status and social factors.

3. RESULTS

3.1 Canonical Correlation Analyses

3.1.1 CCAs without and with genetic background. Figure 3.1.1 displays the overall CCA outcomes, described in this and the next three subsections. Latent variate pairs were retained for analysis if their correlation was significant ($p < .01$ divided by 2, or $p < .005$). This criterion was met for the first two CCA components without genetic background: CCA1 $F(55, 5331) = 9.36$, $p < .001$, $r^2 = .305$; CCA2 $F(40, 4370) = 1.86$, $p < .001$, $r^2 = .036$. This criterion was also met for the first two CCA components with genetic background: CCA1 $F(88, 7537) = 6.52$, $p < .001$, $r^2 = .324$; CCA2 $F(70, 6707) = 1.50$, $p = .004$, $r^2 = .043$.

3.1.2 Stability of CCA solutions. Probes of CCA stabilities illustrate the robustness of especially the first canonical variates. For CCA1, across the 10,000 jackknifed samples, 100% of the resampled outcomes were significant for models without or with genetic background. The range of variance accounted for (99% confidence intervals of r^2 values) by CCA1 was reasonably tight for models both without (.281 to .333) and with (.299 to .353) genetic background. For CCA2, across the resamples, only 83% without and 57% with genetic background met the significance threshold. The 99% confidence intervals of variance accounted for by CCA2 were similarly distributed (without genetic background = .0275 to .0545; with genetic background = .0342 to .0616). Given CCA2's low variance accounted for and questionable stability, it was not further considered.

3.1.3 Comparison of CCA solutions without and with generic background. The next issue is whether the CCA solutions without and with genetic background are structurally similar. Figure 3.1.1 shows the CCA1 loadings for the two models. Adding genetic background increased r^2 of CCA1 by 1.9%, which was not a significant increment (the two r^2 values are captured by the

99% confidence intervals, provided in the above subsection). The canonical loadings are also statistically indistinguishable between models without and with genetic background (the magnitudes of the paired bars are nearly identical, and they are within the 99% confidence intervals for every loading).

Every participant also has a score for both sides of the canonical correlation equation, that is, a score that is a weighted average of the SES/self-identified race side of the equation and a similar weighted score for the bio-factors side of the equation (see Figure 3.1.2 for the bivariate distribution without genetic background). The intra-individual correlations between those corresponding CCA1 variate scores of models without and with genetic background models is .97 for the SES/self-identified race weighted scores and .99 for the bio-factor weighted scores. This outcome suggests that the models have the same structure regardless of genetic background information.

3.1.4 Nature of CCA associations. The direction and magnitude of the canonical loadings support interpretation of the latent variates. To aid interpretations, Figure 3.1.3 (SES) and Figure 3.1.4 (Black, Asian, and Hispanic) show social differences across B-SNIP bio-factors. Figure 3.1.2 shows the scatterplot of the SES/self-identified race variate against the bio-factor variate. As derived from Figure 3.1.1, lower scores on the former variate are most clearly associated with worse SES and being Black. Alternatively, higher scores on the bio-factor variate are most clearly associated with better cognitive performance (especially BACS and Antisaccade bio-factors) and larger event-related potential (ERP) magnitudes, which indicate better ability to respond to salient stimuli. The location of Biotypes and healthy centroids (and standard deviation ellipsoids) are also displayed. Figure 3.1.5 shows this same plot stratified by DSM diagnoses.

3.2 Regression & Mediation Models

These models evaluated the individual relationships between SES, self-identified race, or genetic background and every individual bio-factor. Individual and parental SES, Black and Asian self-identified race, and genetic PC1 were used in these models. The Hispanic, PC2, and PC3 variables made no significant contributions in the CCAs, and therefore were not included (see ([Wang et al., 2020](#))). Being the most general characteristics, individual and family SES were initially added to the social models, followed by the addition of self-identified race, although the results were the same if self-identified race was added first. Genetic background was analyzed separately. Figure 3.2.1 summarizes the outcomes.

BACS, Antisaccade, stop signal task (SST), intrinsic EEG activity (IEA), and ERP magnitudes had statistically significant associations with SES, SES and self-identified race as a combined variable, and PC1. The frontal P300 complex had significant associations only with SES and SES plus self-identified race. The ongoing EEG activity and latency bio-factors showed no significant associations in these models (see Figure 3.2.1). None of the other bio-factors had large proportions of variance accounted for by any of the included variables. Only the BACS showed substantially more than 10% of shared variance between social or genetic background variables and bio-factor scores. Paired ERP, Oddball ERP, and Antisaccade bio-factors had the next highest shared variances with social or genetic background variables (in the 3% to 10% range). IEA, SST, Paired S2 ERP, and the Frontal P300 complex shared variance with social and genetic background variables in 0.5% to 4.5% range. In general, social variables shared larger proportions of variance with bio-factors than did genetic background (see Figure 3.2.1 and Table 3.1.1).

Models were created to evaluate the direct relationship between genetic similarity PCs and every bio-factor, and the possible mediation of those relationships by socio-demographic measures. Casual mediation analyses (Tingley et al., 2014) were computed using R-studio to test for mediation of genetic similarity (linear combination of PC1, PC2, and PC3) by SES (linear combination of individual and family) and self-identified race (combination of Black and Asian; Hispanic was excluded since it made no contribution in the CCAs).

BACS, antisaccade, SST, ERPs, and IEA had statistically acceptable fits. None of the other bio-factors had large proportions of variance account for by any of the included variables. Nevertheless, the significant coefficients and mediation effects suggest that the variables included are relevant and the models capture meaningful relationships (Kang & Ahn, 2021).

SES significantly mediated the direct genetic similarity associations for 8 of the bio-factors: BACS CI[0.39, 0.54], $p < .001$; Antisaccade CI[0.29, 0.56], $p < .001$; SST CI[0.31, 1.0], $p < .001$; PS ERP CI[0.13, 0.24], $p < .001$; OB ERP CI[0.14, 0.26], $p < .001$; Frontal P300 CI[.06, .58], $p = .004$; PS S2 CI[.034, 0.20], $p = .008$; and Latency CI[0.02, 0.28], $p = .004$. The final model included SES and self-identified race, which had significant associations with 10 of 11 bio-factors. SES and self-identified race also significantly mediated the direct genetic similarity associations for 8 of those bio-factors: BACS CI[0.79, 1.0], $p < .001$; Antisaccade CI[0.69, 1.0], $p < .001$; SST CI[0.45, 1.0], $p < .001$; PS ERP CI[0.67, 1.0], $p < .001$; OB ERP CI[0.68, 1.0], $p < .001$; PS P2 CI[0.21, 1.0], $p = .002$; Latency CI[0.07, 1.22], $p = .014$.

It is important to note that because SES, race, and genetic similarity are so confounded with one another, it is not possible to adequately meet the assumptions that mediation models call for. Causal interpretation requires no unmeasured confounding between the variables as well as no reverse causality. Further, it is difficult to satisfy the assumption of sequential ignorability,

which requires that all relevant confounders are controlled for both meditation paths, which is especially difficult to satisfy in observational studies.

High collinearity between the independent variable and the mediator can increase the standard errors of the coefficients associated with the correlated variables, making it difficult to detect significant mediation effects. When the independent variable and the mediating variable are highly colinear, it is difficult for the regression model to determine the unique contribution of each variable to the outcome. This ultimately makes it difficult to detect statistically significant effects and to separate the individual effects on the outcome variable.

3.3 Biotypes and DSM Effects via ANOVAs

The above analyses do not address whether incorporating SES or self-identified race changes the differences between diagnostic groups on bio-factors. Patterns of differences on bio-factors by Biotype and DSM groups have appeared in other publications (Clementz et al., 2022; Parker et al., 2024). This section specifically addresses whether group differences are modified by the inclusion of SES or self-identified race in statistical models. We performed Biotype (Biotype-1, Biotype-2, Biotype-3) by DSM (schizophrenia, schizoaffective, bipolar) ANOVAs that included an additional socio-demographic factor: participant SES, family SES, or self-identified race (Black or Asian). The Hispanic variable was excluded because it made no contribution in the CCAs.

Previous comparisons involving healthy persons showed only main effects of social variables and Healthy versus Psychosis on bio-factors (see Figures 3.1.1, 3.1.3, and 3.1.4). There were no significant interactions. The following analyses did not include the healthy group, but specifically evaluated whether (i) diagnostic group differences were maintained when including

social variables in the ANOVA models, and (ii) there are interactions between social factors and diagnosis.

In the simple models without social variables, Biotypes differ on all bio-factors (see Table 3.1.2), and DSM diagnoses differ on all bio-factors except measures of background EEG activity and saccade latency. Social variables change the nature of these significant main effects, especially for DSM diagnoses (see Table 3.3.1). For Biotypes, 37 of a possible 44 diagnostic group differences (84.1%) were maintained after including social variables in the models. Including Asian in the models had the most significant impact, with SST, Frontal P300, paired stimuli S2 response, and Latency no longer significant. Adding Personal or Family SES also led Frontal P300 (P-SES) and Latency (P-SES and F-SES) to no longer significantly differentiate groups. For DSM, only three of 44 diagnostic group differences (6.8%) were significant after including social variables. If the total is restricted only to the bio-factors that differentiated in simple DSM models, three of 28 tests survived adding social variables (10.7%). The two bio-factors that survived in DSM comparisons are BACS (SES-F and Black) and Antisaccade (SES-F). There was only one significant interaction out of 88 total, for Oddball ongoing activity in the DSM by Black model.

4. DISCUSSION

In this paper, I probed the relationships between and influence of socioeconomic status (SES), race, ethnicity, and genetic similarity to cognitive and neurophysiological features that define psychosis Biotype subgroups. SES and race are related to health disparities, influence medical diagnosis and treatment access, and correlate with brain measures linked to presence or risk for serious psychiatric conditions. There are three main outcomes of this project: (i) SES, self-identified race, and genetic background are related to bio-factor scores, especially cognitive performance and EEG/ERP magnitudes; (ii) genetic background adds little beyond social information to the prediction of bio-factors; and (iii) adding SES and self-identified race to ANOVA models largely maintains bio-factor differences between B-SNIP psychosis Biotype groups, but largely eliminates such differences between DSM psychosis diagnostic groups.

The structural similarity between CCA models with and without genetic similarity was evident; canonical loadings for CCA1 were statistically indistinguishable between the model with and without genetic similarity components included. This suggests that adding genetic similarity variables does not significantly enhance the explanatory power beyond what is captured by socio-demographic variables alone.

Interpretation of the canonical loadings indicates that lower SES and being Black are associated with lower scores on the SES/self-identified race/genetic similarity variate. These scores correlate with poorer cognitive performance and smaller ERP magnitudes, implying reduced responsiveness to stimuli. These findings align with established literature that associates socio-economic disadvantage with poorer cognitive outcomes and neural responsiveness. The similarity in R-squared values for CCA1, regardless of adding genetic information into the model, suggests that socio-demographic factors alone provide ample reasoning for the observed

variance in bio-factor scores. This is reinforced by the high correlation between the CCA1 variates from models with and without genetic information (.97 for SES/self-identified race and .99 for bio-factors). Stability analyses showed that CCA1 was consistently significant across 10,000 jackknifed samples, with tight confidence intervals for variance explained, indicating the robustness of CCA1.

SES, self-reported race, and genetic similarity were considered as individual predictors of bio-factor scores in linear regression models; bio-factors with the most important roles in differentiating Biotype groups had the most substantial individual associations with sociodemographic variables. This includes the BACS, with approximately 25% of variance accounted for, antisaccade and ERPs with the next highest associations ranging from 8% to 10%, followed by SST, IEA, and paired S2 ranging from 3% to 4%. SES and self-reported race (either Black or Asian) together accounted for 31% of the total bio-factor performance variance. Event-related potential magnitudes – which measure an individual’s ability to register stimulus salience – along with cognitive performance made the largest contributions to these associations. SES alone had significant associations with bio-factors, but adding self-reported race to the model enhanced the associations for IEA and ERPs. This indicates that although SES is a significant contributor, self-reported race strengthens this association further. This could be due to factors such as implicit racial bias and stress contributing to a person's health and development (Letang et al., 2021) that may not be captured by SES alone. Additionally, these findings show that genetic similarity had more modest associations with bio-factors when compared to socio-demographics. This supports the notion that sociodemographic features explain more variance in bio-factor scores than does genetic similarity. It is also possible that these modest associations

driven by genetic similarity can be explained, in part, by implicit bias since these components typically align with one's racial phenotype.

Mediation analyses revealed that socio-demographic factors (SES and self-identified race) significantly mediate the relationship between genetic similarity and bio-factor scores. SES had significant direct associations with nine bio-factors and mediated genetic similarity associations for eight of these bio-factors. When both SES and self-identified race were included in the model, they were significantly associated with 10 out of 11 bio-factors and mediated genetic similarity associations for eight bio-factors. This highlights the critical role of socio-demographic variables in understanding the impact of genetic similarity on bio-factors.

Despite the shared variance between socio-demographics and bio-factors, differentiation of Biotypes was largely maintained, even after including SES and self-reported race in ANOVA models. The only bio-factors affected are those that make the most modest contributions to differentiations of Biotypes. The affected bio-factors are also the ones that capture the defining physiological features of Biotype 3, deviations in stimulus salience.

This project is limited by the fact that our sample is not an epidemiological one, ergo, we do not have sufficient representation of all self-reported racial groups, especially as a function of socioeconomic status. Further, we do not have a complete representation of the full genetic similarity spectrum, knowledge of the perception of individuals by others, nor information on actual healthcare disparities by individual. We do not have sufficient data on the amount of time individuals spent in different types of environments during development or the specific types of advantage or disadvantages they might have experienced. Considerations for future research should include the potential effects of early life disadvantage and access to diverse education opportunities and healthcare.

Previous research has concluded that structural racism and socioeconomic disadvantage disproportionately affect Black people. It has also been concluded that Black people receive psychosis diagnoses at higher rates than White people and are less likely to receive an affective disorder diagnosis such as bipolar disorder or depression than are White people. Perhaps these disparities are at least in part due to stereotypes and implicit biases as diagnoses based on clinical interview are inherently subjective. The findings of these analyses provide important implications for future research in populations with serious psychiatric conditions. The significant role that SES and race have in mediating the effects of genetic influence on bio-factors highlights the importance of considering sociodemographic features and social disadvantage when investigating the underpinnings of psychosis neurobiology. Further, the reliability of B-SNIP biotypes even when accounting for race and SES in statistical models suggests that using these laboratory-based measures rather than relying on clinical phenomenology alone may be more meaningful in classifying and treating idiopathic psychoses. Utilizing laboratory-based measures of neurobiology may be the next best step for the field of psychiatry to better assess and treat these illnesses with more objectivity and equity, especially for our underrepresented and underserved patients.

Table 2.1.1 Demographic and Clinical Characteristics By Biotype

Characteristic	Overall N = 2174	Biotype 1 N = 495	Biotype 2 N = 480	Biotype 3 N = 514
Mean Age (SD)	37 (12)	38 (13)	39 (12)	35 (12)
Mean SES (SD)				
Proband	43 (16)	50 (14)	40 (12)	43 (15)
Family	40 (16)	44 (16)	43 (16)	37 (16)
Mean Symptom Score (SD)				
PANSS Positive	16 (6)	16 (6)	17 (6)	14 (6)
PANSS Negative	15 (6)	15 (6)	16 (6)	14 (6)
MADRS	13 (10)	13 (10)	13 (10)	12 (9)
YMRS	9 (7)	9 (7)	10 (8)	9 (7)
Birchwood Social	133 (27)	121 (24)	119 (24)	130 (24)
Ethnicity				
Not Hispanic	87%	87%	87%	88%
Hispanic	13%	13%	13%	12%
Race				
Black	34.9%	49.5%	41.9%	22.8%
American Indian	0.3%	1.0%	0.2%	0.2%
Asian	4.6%	3.6%	1.5%	3.7%
White	52.8%	38.8%	48.1%	65.2%
Multiracial	4.5%	4.6%	5.2%	4.7%
Other	2.9%	2.4%	3.1%	3.5%

Table 2.1.2 Demographic and Clinical Characteristics by DSM Diagnosis

Characteristic	Overall N = 2174	Schizophrenia N = 495	Bipolar Disorder N = 480	Schizoaffective Disorder N = 514
Mean Age (SD)	37 (12)	38 (12)	36 (12)	39 (12)
Mean SES (SD)				
Proband	43 (16)	52 (14)	42 (15)	48 (14)
Family	40 (16)	43 (16)	38 (16)	43 (16)
Mean Symptom Score (SD)				
PANSS Positive	16 (6)	17 (6)	13 (5)	18 (6)
PANSS Negative	15 (6)	17 (6)	12 (5)	15 (6)
MADRS	13 (10)	10 (8)	14 (10)	15 (10)
YMRS	9 (7)	9 (6)	8 (8)	11 (7)
Birchwood Social	133 (27)	118 (23)	135 (23)	120 (25)
Ethnicity				
Not Hispanic	87%	86%	87%	88%
Hispanic	13%	14%	13%	12%
Race				
Black	34.9%	88.3%	19.2%	40.6%
American Indian	0.3%	0.5%	0.5%	0.4%
Asian	4.6%	3.8%	2.3%	2.4%
White	52.8%	39.0%	72.1%	46.1%
Multiracial	4.5%	4.3%	3.2%	7.1%
Other	2.9%	3.0%	2.7%	3.3%

Table 3.2.1 Linear Regression Statistics

Biofactor	SES			SES+SRR			Genetic PCA Components		
	R ²	R ² -Adj.	p	R ²	R ² -Adj.	p	R ²	R ² -Adj.	p
BACS	.238	.237	<.001***	.2653	.2636	<.001***	.115	.114	<.001***
Antisaccade	.077	.071	<.001***	.085	.083	<.001***	.040	.039	<.001***
SST	.033	.032	<.001***	.034	.031	<.001***	.008	.007	<.001***
PS ERP	.031	.030	<.001***	.079	.077	<.001***	.073	.073	<.001***
OB ERP	.001	-.0004	.4925	.007	.005	.02*	.089	.088	<.001***
IEA	.009	.008	<.001***	.044	.042	<.001***	.045	.044	<.001***
PS Ongoing	.00005	-.0012	.9614	.006	.003	.0531	.005	.004	.004**
OB Ongoing	.0009	-.0004	.4925	.007	.005	.0194*	.004	.003	.011*
P300	.007	.006	.0025**	.010	.007	.0024*	.005	.005	.003**
PS P2	.013	.013	<.001***	.037	.034	<.001***	.031	.031	<.001***
Latency	.072	.071	<.001***	.007	.004	.0270*	.0005	-.0006	.7705

Linear Regression Results. The table above shows multiple and adjusted R² values and associated *p*-values resulting from multiple linear regressions run using genetic PCA component 1, SES, and SES+SRR combined for each of the 11 biofactors. SES = Socio-Economic Status, SRR = Self-Reported Race, R² = R-Squared, R²-Adj = R-Squared Adjusted

Table 3.3.1 Biotype and DSM by Socio-Demographics Effects on Bio-factors

<i>Bio-factors</i>	<i>Biotype Alone p-value</i>	<i>Biotype SES-P p-value</i>	<i>Biotype SES-F p-value</i>	<i>Biotype Black p-value</i>	<i>Biotype Asian p-value</i>	<i>DSM Alone p-value</i>	<i>DSM SES-P p-value</i>	<i>DSM SES-F p-value</i>	<i>DSM Black p-value</i>	<i>DSM Asian p-value</i>
BACS										
Main	<.001	<.001	<.001	<.001	<.001	<.001	.013	<.001	<.001	.084
Inter	---	.657	.514	.177	.419	---	.258	.816	.656	.488
Antisaccade										
Main	<.001	<.001	<.001	<.001	.003	<.001	.035	<.001	.021	.069
Inter	---	.904	.273	.990	.940	---	.269	.067	.155	.071
SST										
Main	<.001	<.001	<.001	<.001	.544	.001	.545	.603	.646	.076
Inter	---	.565	.074	.093	.372	---	.502	.286	.639	.121
IEA										
Main	<.001	<.001	<.001	<.001	<.001	.902	.245	.586	.782	.789
Inter	---	.508	.487	.140	.092	---	.211	.314	.107	.688
PS Ongoing										
Main	<.001	<.001	<.001	<.001	<.001	.974	.722	.068	.192	.352
Inter	---	.324	.813	.045	.661	---	.870	.288	.235	.297
OB Ongoing										
Main	<.001	<.001	<.001	<.001	<.001	.947	.797	.193	.683	.388
Inter	---	.845	.471	.144	.834	---	.851	.712	.644	.435
PS ERP										
Main	<.001	<.001	<.001	<.001	<.001	.002	.898	.151	.194	.874
Inter	---	.974	.248	.140	.227	---	.896	.947	.281	.569
OB ERP										
Main	<.001	<.001	<.001	<.001	<.001	.009	.256	.020	.211	.720
Inter	---	.863	.445	.403	.046	---	.304	.314	.008	.435
Frontal P300										
Main	<.001	.036	<.001	<.001	.015	<.001	.742	.687	.595	.984
Inter	---	.185	.072	.984	.367	---	.947	.990	.235	.839
PS S2										
Main	<.001	<.001	<.001	<.001	.041	<.001	.019	.113	.237	.004
Inter	---	.397	.818	.621	.226	---	.192	.307	.028	.050
Latency										
Main	<.001	.077	.018	<.001	.190	.026	.345	.864	.194	.846
Inter	---	.862	.812	.325	.122	---	.628	.479	.896	.062

Figure 3.1.1

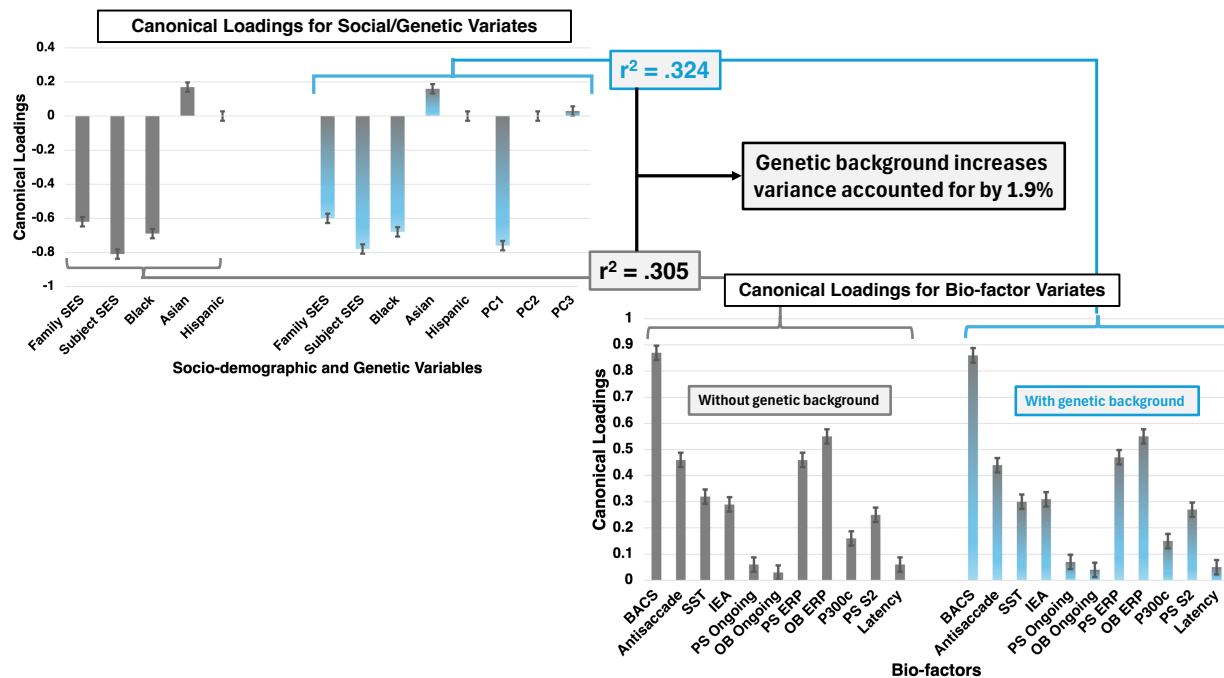


Figure 3.1.2

Canonical Correlation Variates Scatter Plot

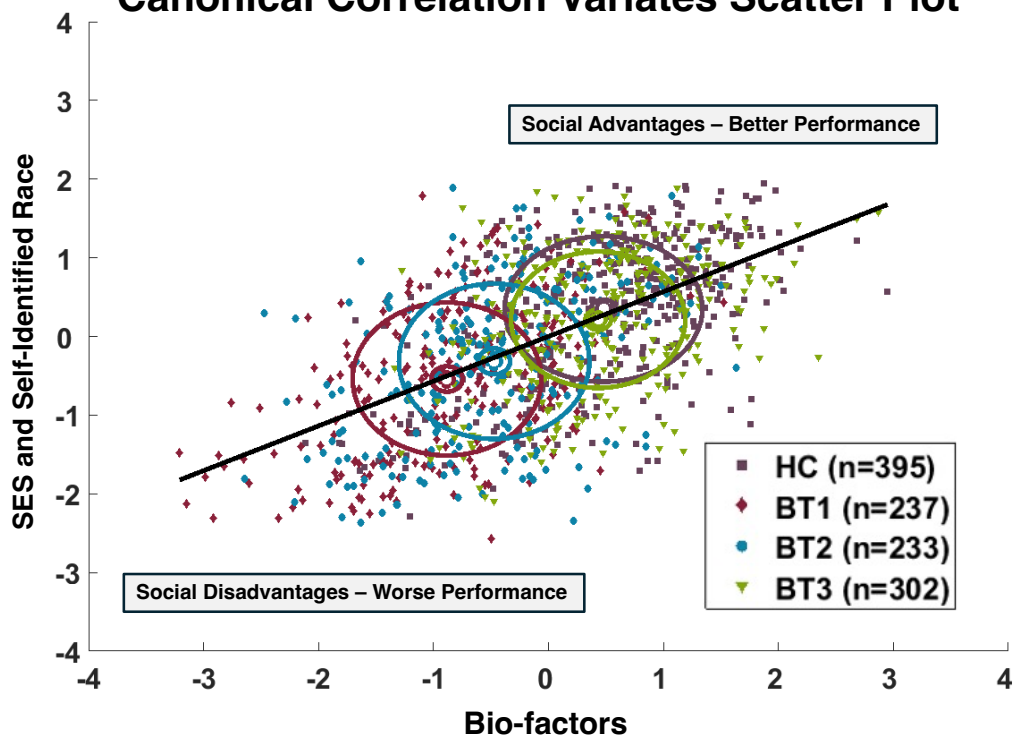


Figure 3.1.3

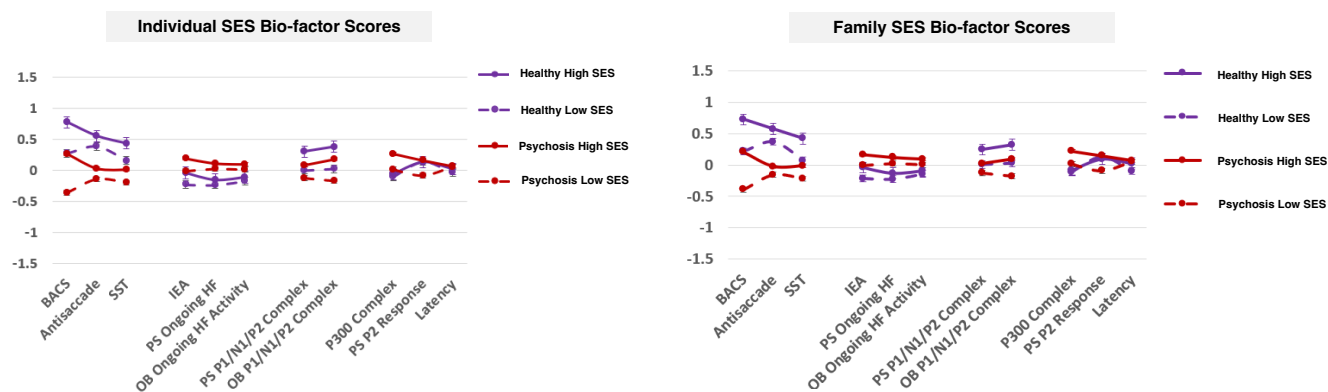


Figure 3.1.4

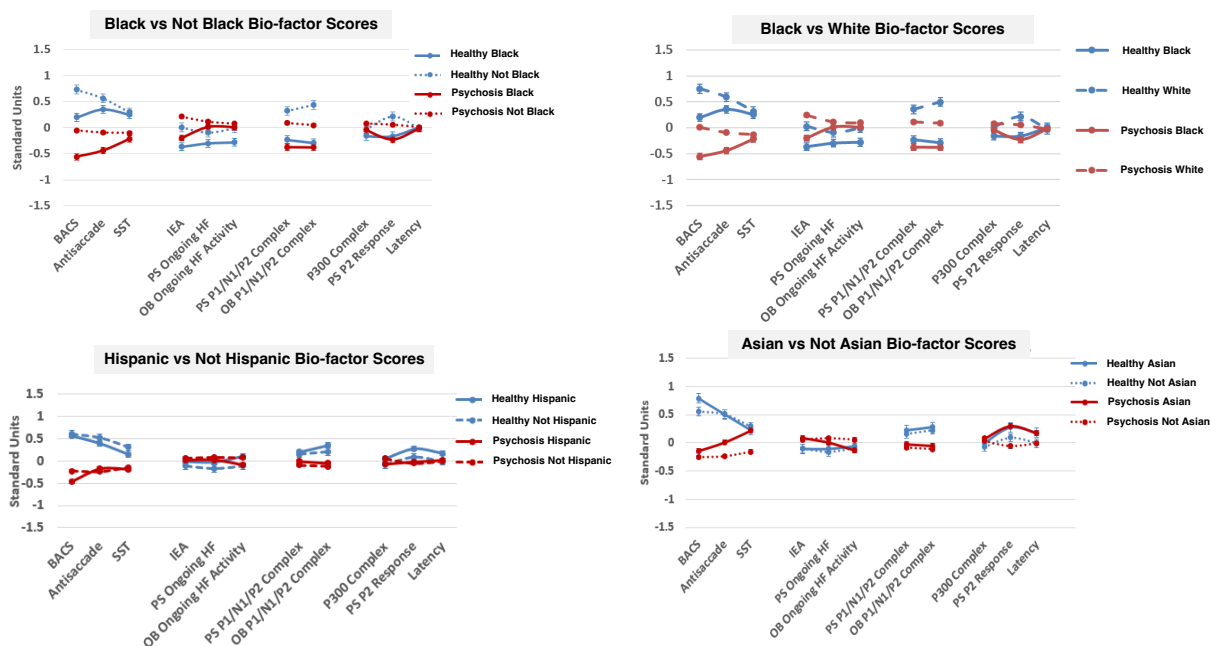


Figure 3.1.5

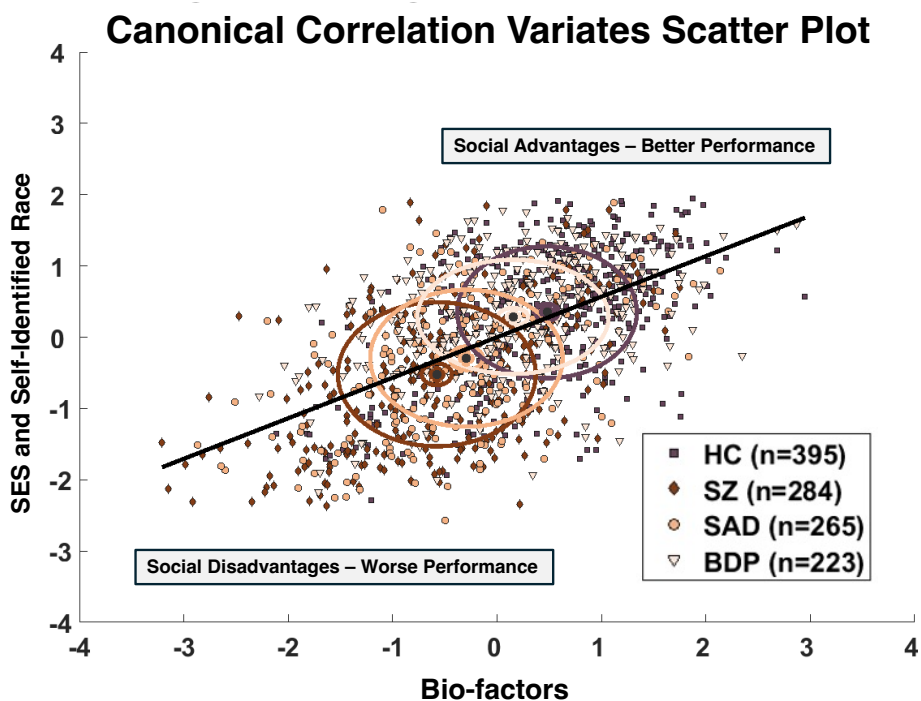
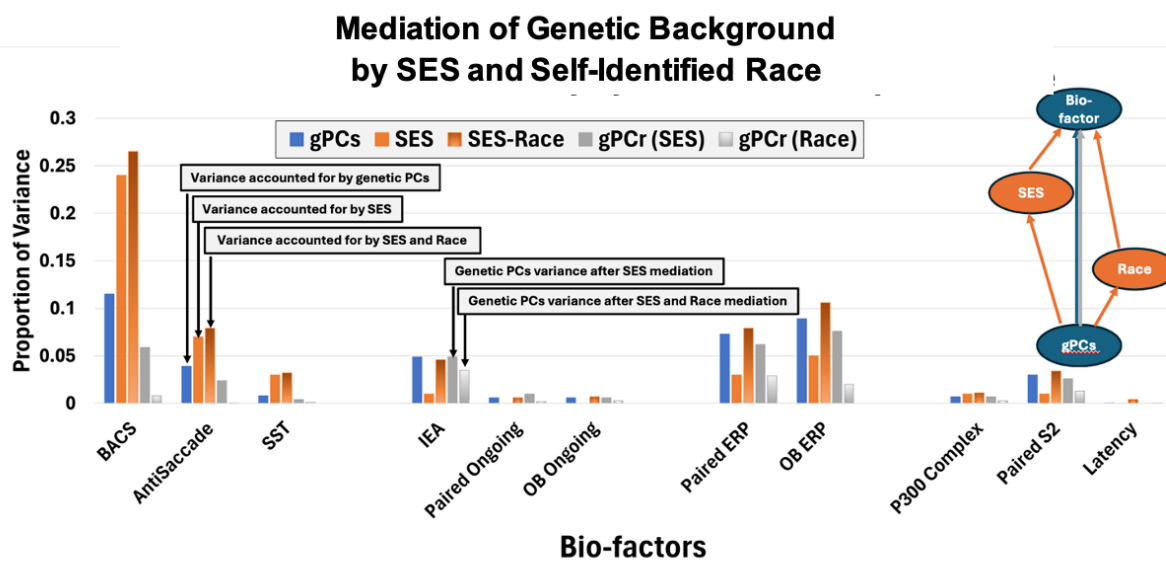


Figure 3.2.1



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